Southern Medical Journal

JOURNAL OF THE SOUTHERN MEDICAL ASSOCIATION

VOL. 54 JULY 1961 NO. 7

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Fifty-Fifth Annual Meeting, November 6-9, 1961, Dallas, Texas

JULY 1961

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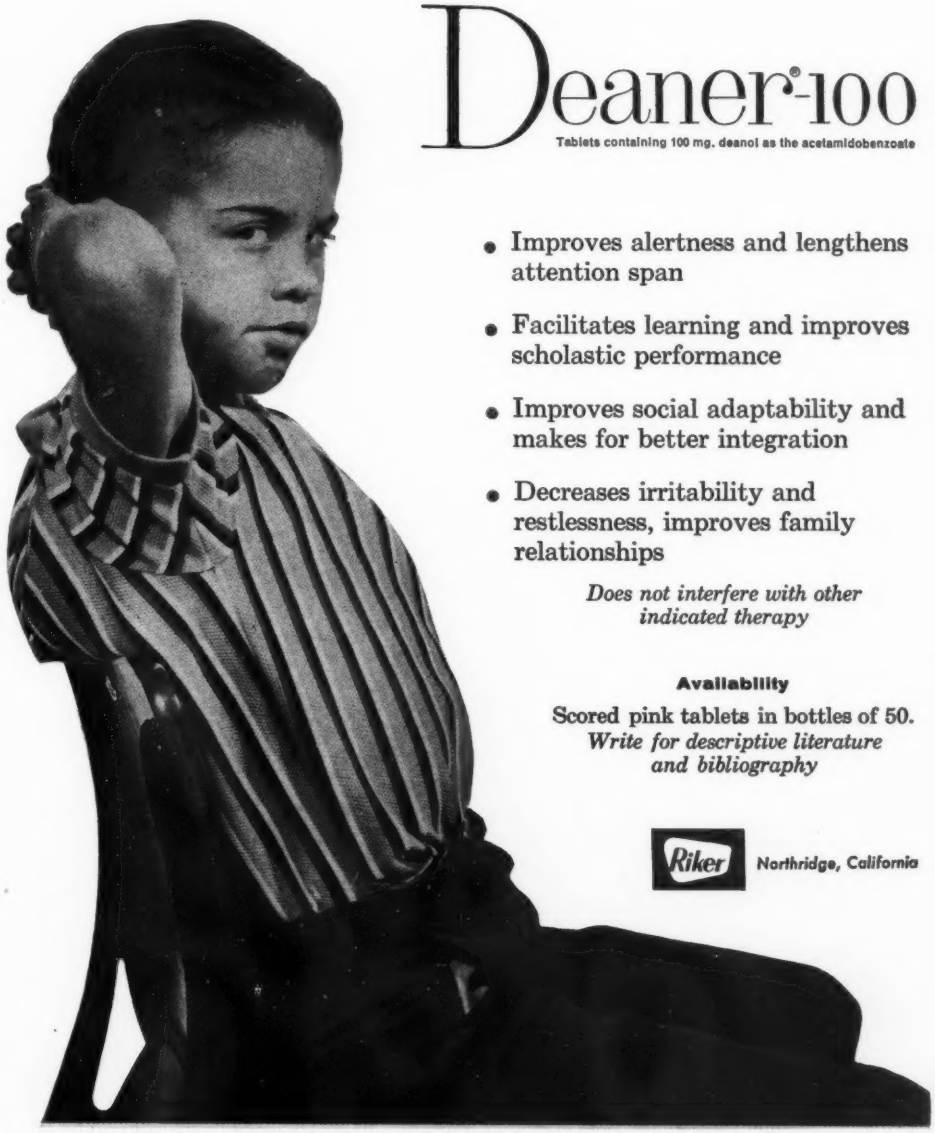

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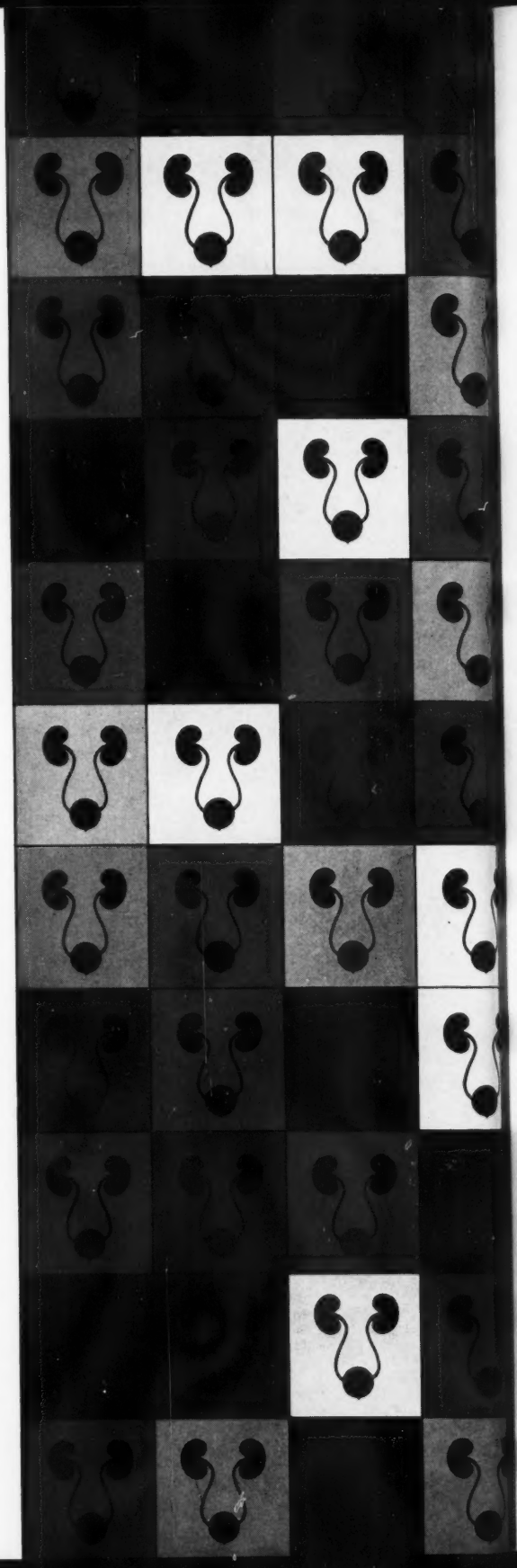

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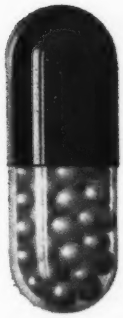

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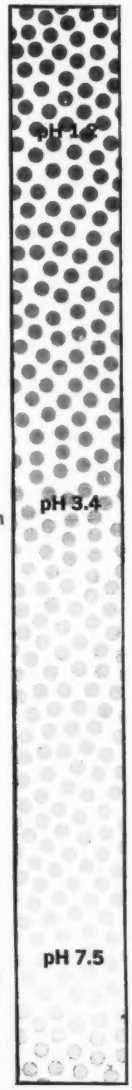

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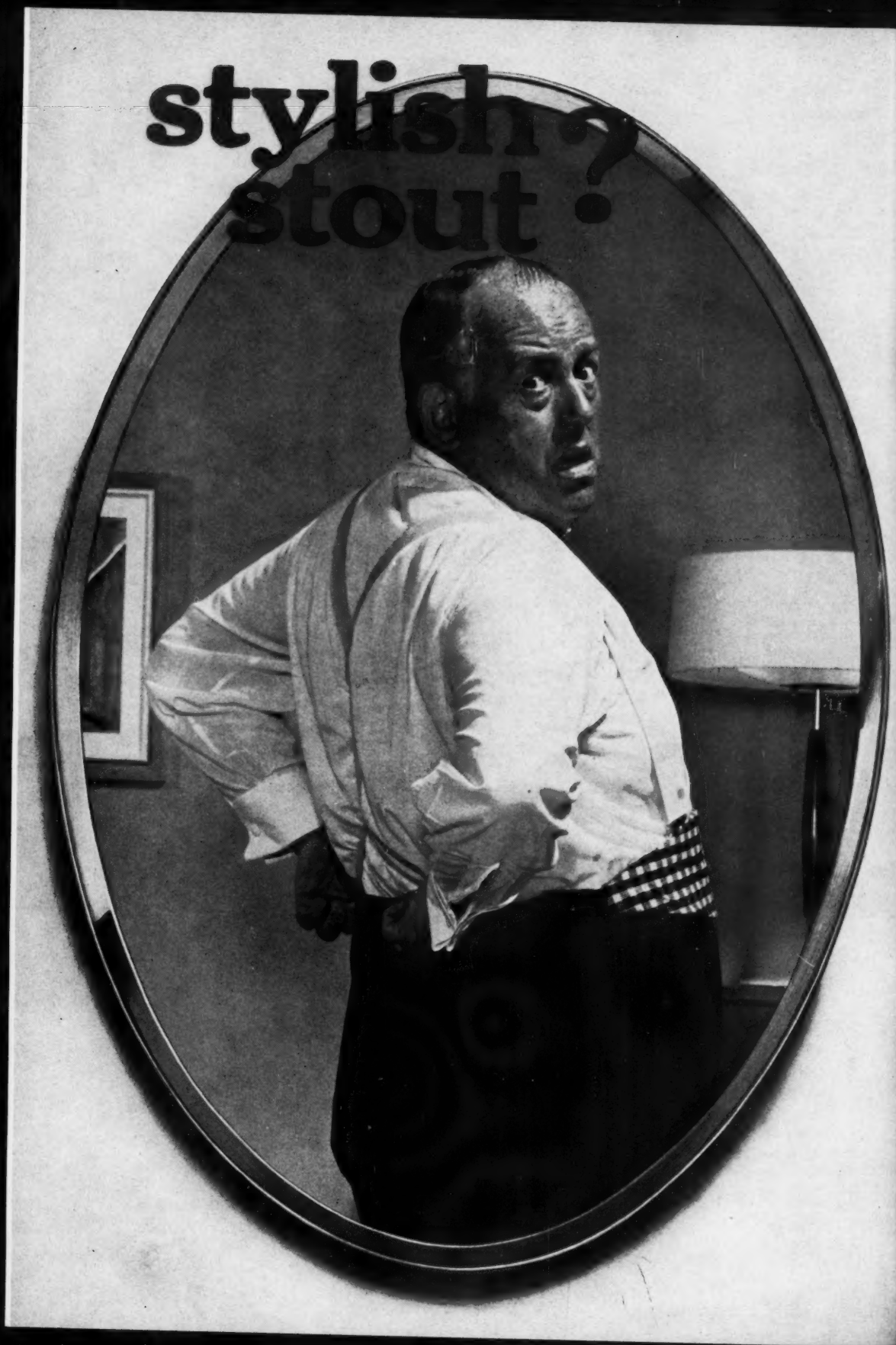
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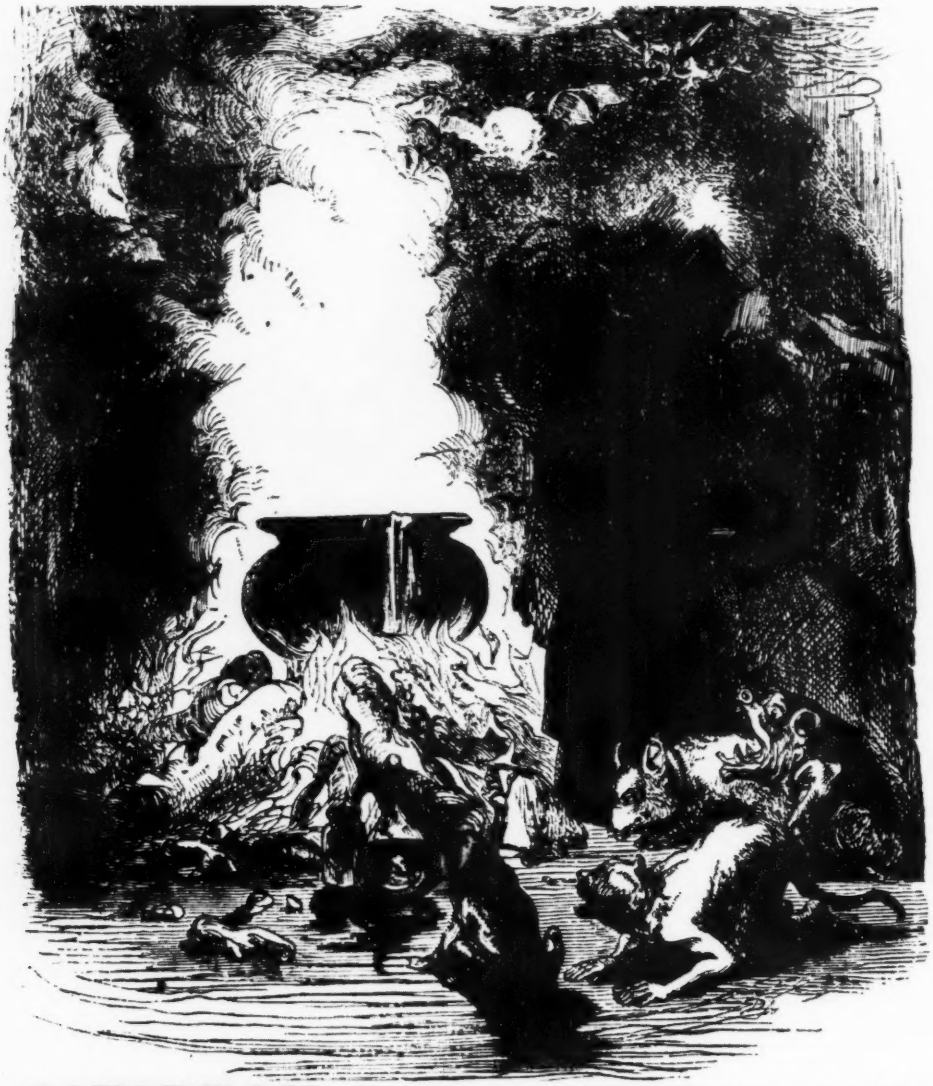

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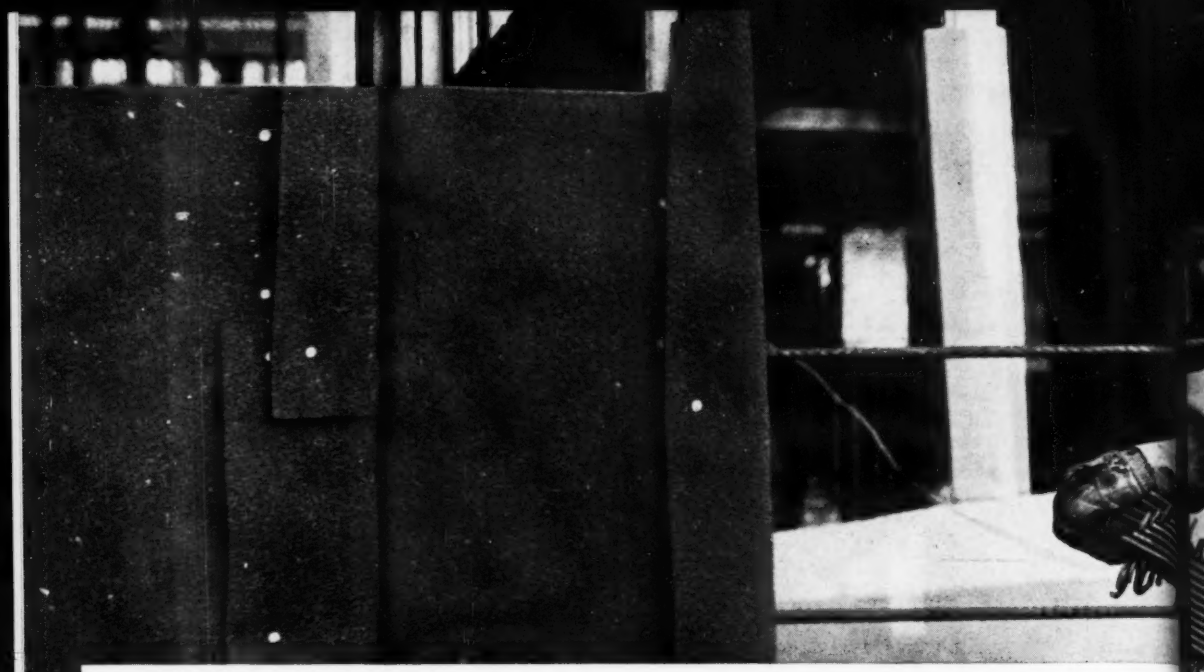

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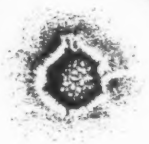

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Dosage: Two to six Maroon & White capsules daily, or as directed by a physician.

Availability: Apothecary jars of 100, also bottles of 1000.

Reference: (1) Terry, G. Texas State Journal of Medicine Vol. 53 pp 829 (1957)

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References: 1. Garber, R. C.: J. Florida M. A. *45*:549 (Nov.) 1958. 2. Lipton, M. I.: Pennsylvania M. J. *64*:60 (Jan.) 1961. 3. Ayd, F. J., Jr.: Psychotropic Drugs, S. Garattini and V. Ghetti, eds., New York, Elsevier Publishing Co., 1957, p. 548. 4. McGettigan, D. L.: West. Med. *1*:8 (Jan.) 1960.

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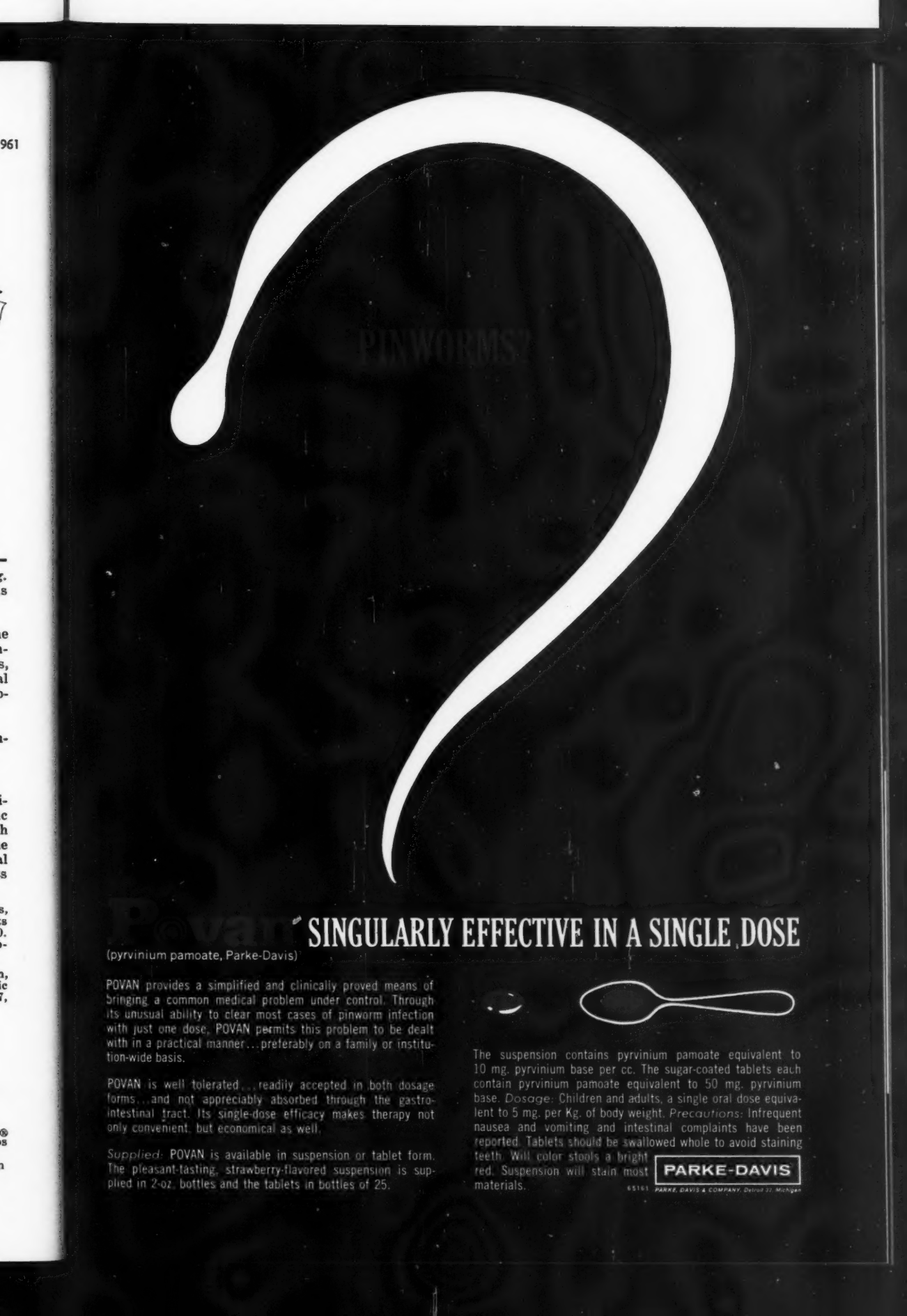
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1. Beckman, H.: *Pharmacology: The Nature, Action and Use of Drugs*, 2nd Ed. W. B. Saunders Company, Philadelphia and London, 1961, p. 673.

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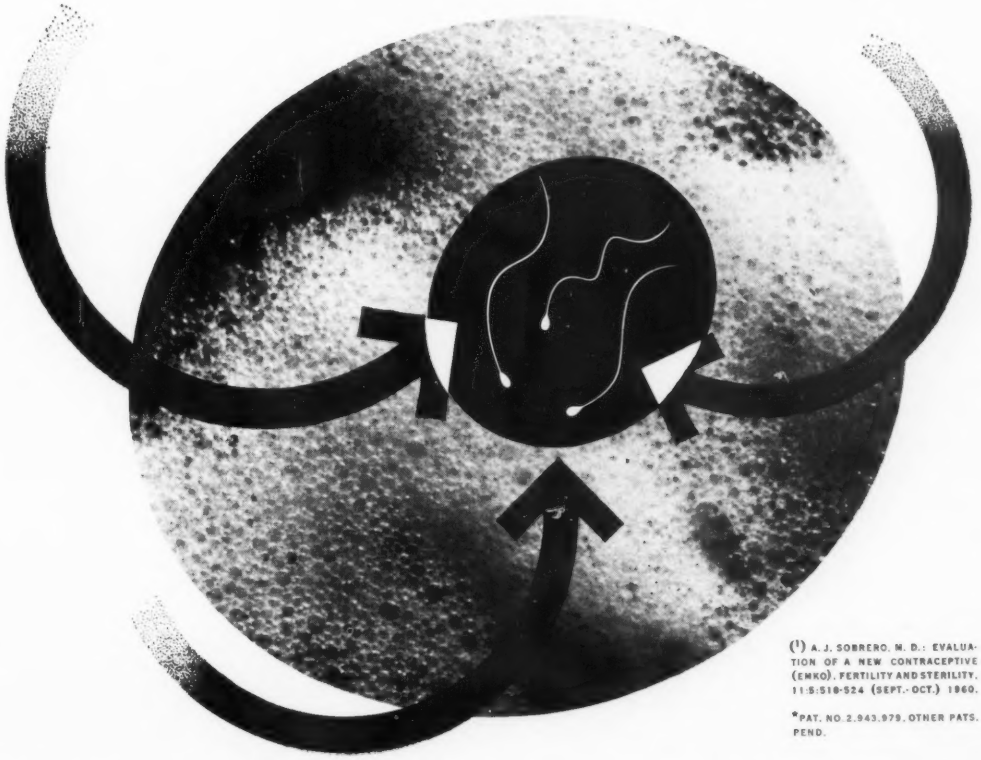

(1) A. J. SOBRERO, M. D.: EVALUATION OF A NEW CONTRACEPTIVE (EMKO). FERTILITY AND STERILITY, 11:5:518-524 (SEPT.-OCT.) 1960.

*PAT. NO. 2,943,979. OTHER PATS. PEND.

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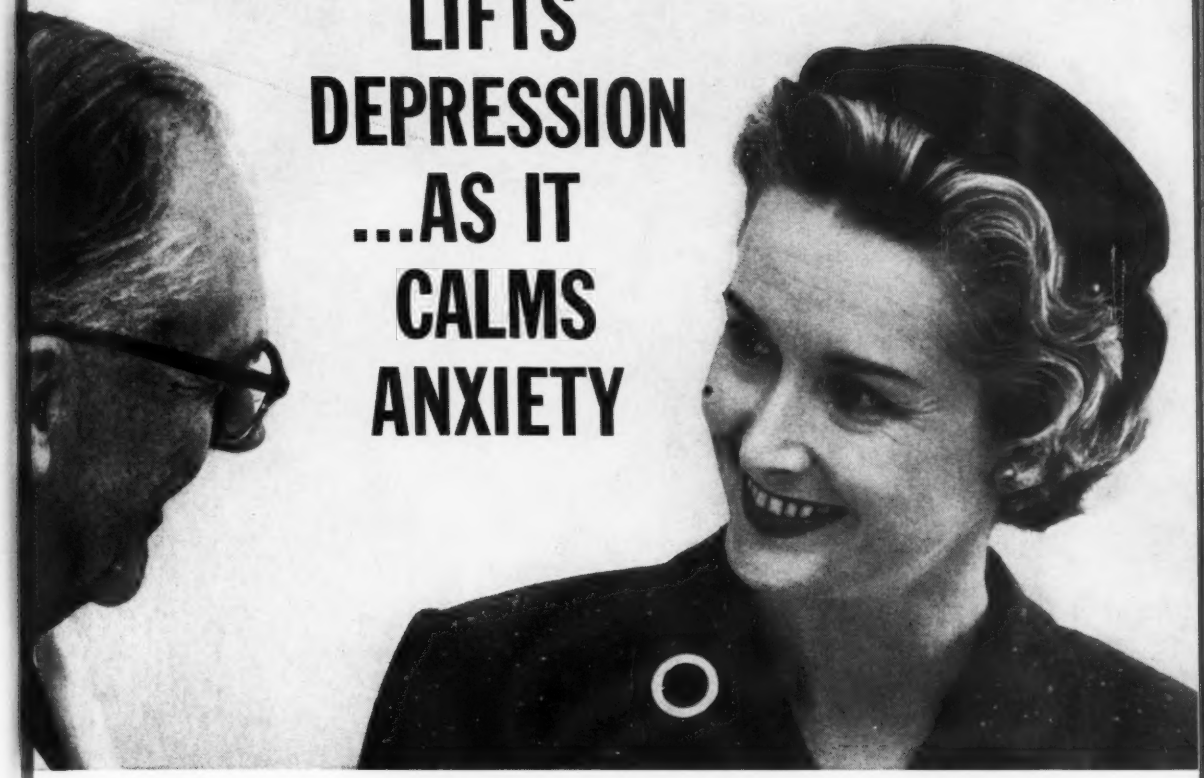

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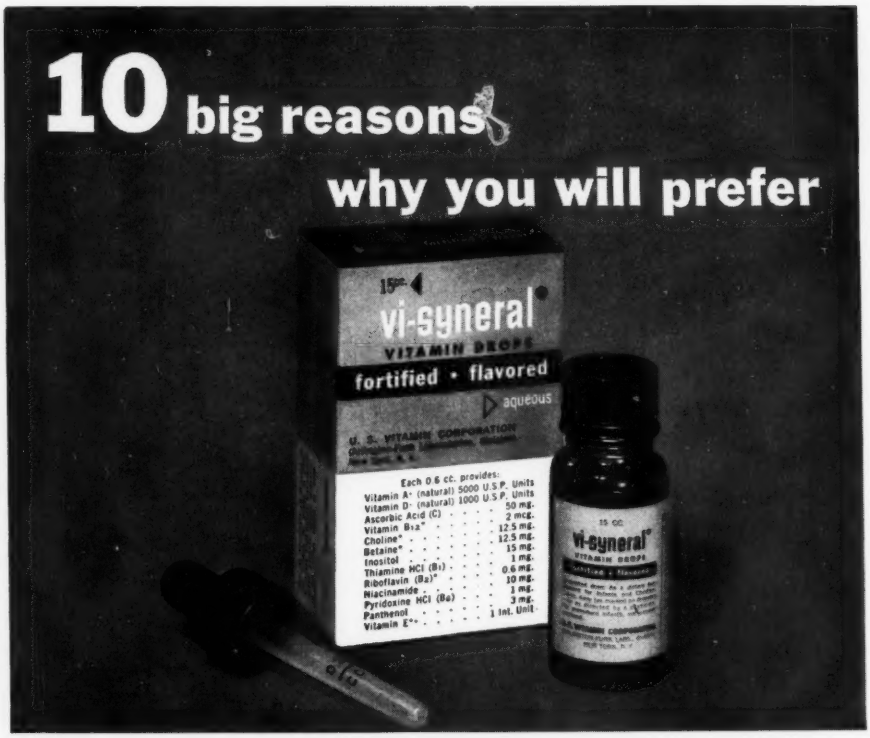

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1. J. Pharm. & Exp. Ther. 89:131
2. J. Urology 73:487
3. J. Mo. Med. Assoc. 48:685
4. Med. Rec. & Annals 43:1104

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References: 1. Spielman, A. D.: Evaluation of a Combination Tablet of Theophylline, Ephedrine Sulphate, Phenobarbital, Thenyldiamine and Glyceryl Guaiacolate in the Treatment of Chronic Asthma, Ann. Allergy 18:281, 1950. 2. Waldbott, G.: Bronkotabs – a New Antiasthmatic Preparation (Preliminary Report), Int. Arch. Allergy 17:116, 1960.

For full information on Breon's five antiasthmatics, see pp. 538-539 of the 1961 PHYSICIANS' DESK REFERENCE plus the 2nd, 3rd, or 4th quarterly supplement.

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(1) Danowski, T. S.: Diabetes Mellitus, Baltimore, Williams & Wilkins, 1957, p. 239. (2) McCune, W. G.: M. Clin. North America 44:1479, 1960. (3) Ackerman, R. F., **et al.**: Diabetes 7:398, 1958.

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References: 1. Curran, T. R., and Phelps, D. K.: Am. Pract. & Dig. Treat. *11:* 617, 1960. 2. Levy, S.: J.A.M.A. *153:* 1260, 1953. 3. Connolly, R.: W. Va. Med. J. *56:* 263, 1960.

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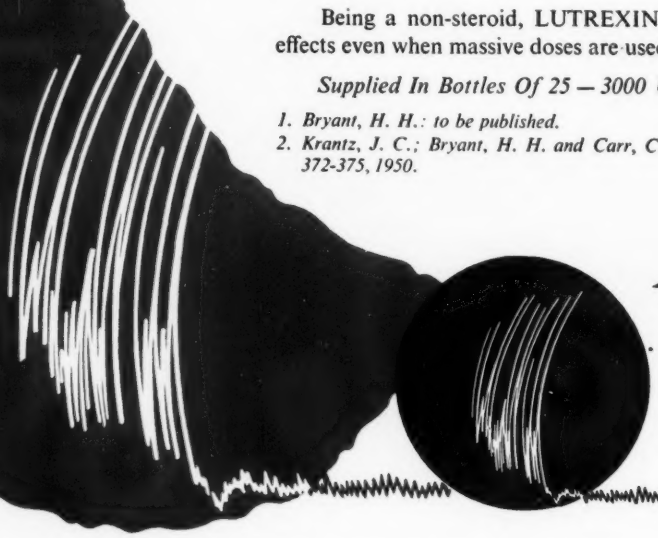
1. Bryant, H. H.: to be published.
2. Krantz, J. C.; Bryant, H. H. and Carr, C. J.; Surg., Gyn. & Obst., 90: 372-375, 1950.



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Southern Medical Journal

PUBLISHED BY SOUTHERN MEDICAL ASSOCIATION

July 1961

Changing Trends in the Surgical Treatment of Diverticulitis of the Colon*

ROBERT W. BARTLETT, M.D.,† *St. Louis, Mo.*

The surgical treatment of the complications of diverticulitis is well established. In considering the complications and diagnostic problems, the author raises for serious consideration elective surgery in uncomplicated cases to forestall the difficulties which may arise at a future date, and the need for operation as an emergency procedure.

THE DISEASE ENTITY DIVERTICULITIS becomes increasingly more important as its incidence rises with the ever-increasing extension of man's life expectancy. As pointed out by Welch and his associates,[1,2] in their analyses from the Massachusetts General Hospital, approximately 10% of individuals over the age of 40 exhibit diverticula and about 20% of these develop clinical diverticulitis. The highest incidence of diverticulosis and diverticulitis is to be found in the sixth, seventh, and eighth decades, at which time the latter lesion rivals carcinoma in importance as a disease of the colon.

In considering the therapy of diverticulitis one recognizes the fact that except in the mild or moderate cases of reasonably short duration, there has been a sharp swing in the past few years to definitive surgical treatment for at least three very good reasons. These are, first of all, a better appreciation of the severity of the complications when through procrastination a physician permits them to develop; second, the increasing frequency of the disease in an aging population; and third, the relative safety of elective resections of the colon today.

*Read before the Section on Surgery, Southern Medical Association, Fifty-Fourth Annual Meeting, St. Louis, Mo., Oct. 31-Nov. 3, 1960.

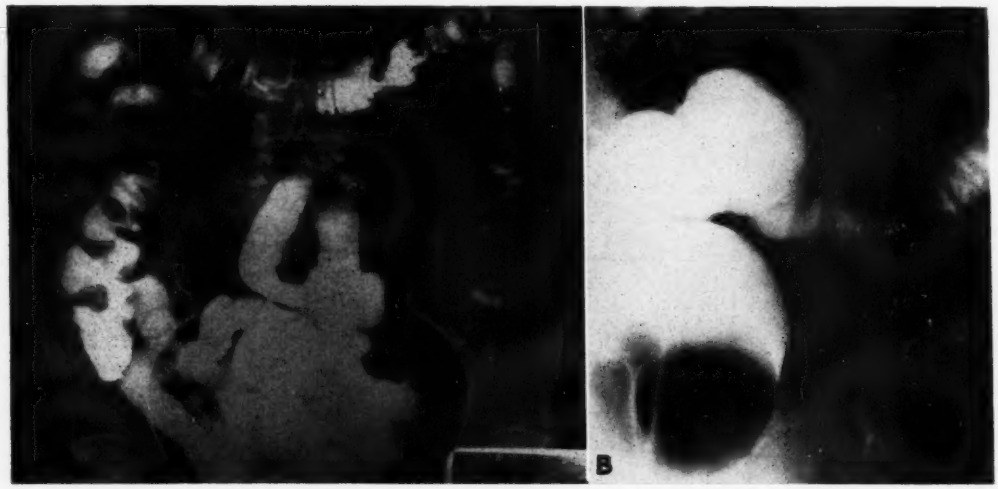
†From the Department of Surgery, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

Uncomplicated Disease

We are all agreed that surgery must be carried out for the complications of diverticulitis, as will be discussed later; however, a strong case can be made for definitive surgery as the treatment of choice in certain of the uncomplicated cases, such as when there are repeated episodes of inflammation, under which circumstances there is a direct relationship of frequency of attacks to the development of serious complications. Then, too, the pain, morbidity and consequent financial loss associated with recurring illness become very important to the victim himself, who usually welcomes a quick and lasting end to his troubles through surgery (Figs. 1 and 2).

Another group in the uncomplicated category who should be advised to have operation are patients demonstrating severe persistent deformity of the sigmoid on barium enema x-ray examination. This is the result of major organic changes rather than enterospasm and strongly suggests the probability of later major complications unless elective prophylactic resection is carried out. A word of warning should also be given regarding the patient who develops urinary symptoms in association with diverticulitis, for these may be the first indication of a later vesicosigmoid fistula unless forestalled by prompt surgical intervention.

FIG. 1



Uncomplicated chronic diverticulitis. A woman, aged 70, had repeated episodes of fever, L.L.Q. tenderness and mild cramps. Evacuation film (A) shows multiple diverticula of sigmoid. Barium enema film (B) demonstrates fringed contour, edema of mucosa and diverticula of sigmoid lesion. Anterior resection of sigmoid resulted in complete cure.

Complications of Diverticulitis and Treatment

In discussing the complications of diverticulitis, let us first consider obstruction which is most apt to be chronic in nature with episodes of rather acute symptoms interspersed with periods of relative freedom. Eventually, however, an acute complete obstruction will occur necessitating a transverse colostomy for emergency relief. At this point I would like to emphasize the fact that the only satisfactory type of colostomy for obstruction or perforation is a completely diverting one, and this can only be attained by completely dividing the loop of transverse colon, thus avoiding spill-over into the distal segment of bowel (Fig. 3).

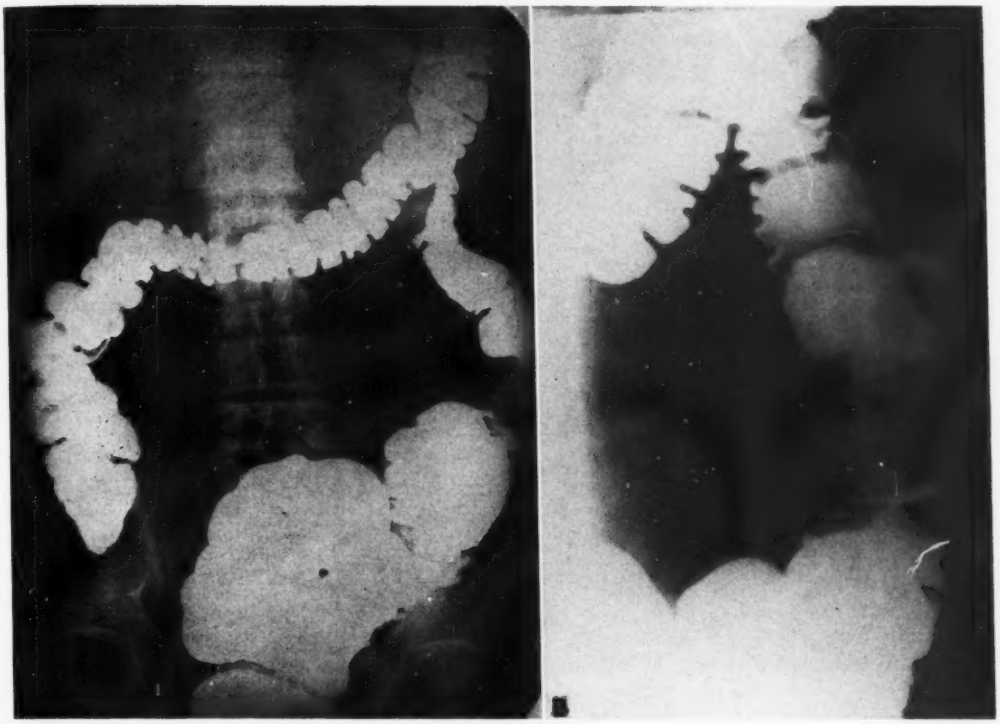
In diverticulitis the edema of inflammatory origin ordinarily subsides within a week or so, to the extent that the acute obstruction is relieved; however, this is not apt to be true when carcinoma happens to be the source of the acute block. Therefore, when the obstruction persists and barium enema x-ray studies are equivocal, the colon should be prepared and resection carried out promptly without waiting the usual 6 weeks following colostomy for clear-cut diverticulitis.

In further reference to carcinoma, it should be pointed out that while diverticulitis and cancer may be coexistent occasionally in the same colon, there is no evidence that the

FIG. 2

Uncomplicated chronic diverticulitis. A woman, aged 51, had recurring inflammatory signs and symptoms in the L.L.Q. Barium enema films show multiple diverticula in all segments of the colon. Extensive subtotal colectomy with low ileosigmoidostomy gave complete relief of symptoms.

FIG. 3



Chronic diverticulitis with complication of obstruction. A man, aged 48, had symptoms of partial low intestinal obstruction relieved on conservative therapy. Barium enema films (A and B) then disclosed filling defect in low descending colon due to chronic diverticulitis though carcinoma was suspected. Resection led to recovery.

former predisposes in the slightest degree to the development of the latter. The pitfall, of course, is that the differential diagnosis can not always be made preoperatively between the two lesions, and when an error is made regarding the correct diagnosis of cancer a most unfortunate delay in therapy may result.

Acute perforations generally produce either a walled-off abscess with a tender mass or a free perforation with all of the signs of general peritonitis. Small pericolic abscesses will often evacuate themselves into the colon and subside under conservative treatment, whereas the occasional large abscess may require drainage plus transverse colostomy. The free perforation must be closed and/or drained and must likewise have the diverting colostomy as a life-saving measure and as the preliminary step to eventual resection. Perforations into other viscera, especially the bladder in the male, are very troublesome and also require multiple stage operation for their cure.

A good deal has been written about bleeding with diverticulitis, but certainly the patient with daily blood-streaked stools is much more apt to be suffering from a carcinoma or polyp than from diverticulitis. It goes without saying that proctosigmoidoscopic examination would lead quickly to the correct diagnosis if ulcerative colitis were the cause of the bleeding. Massive hemorrhage does occur occasionally, however, as a result of diverticulitis, particularly in the older age groups and the exact location of the bleeding point is almost impossible to identify. Blind resection of the sigmoid segment is sometimes performed as an emergency measure; however, the risk is considerable since one is dealing with an unprepared colon in a patient who is apt to be in rather poor condition at the moment. The alternative to this is a completely diverting transverse colostomy which is a far less formidable procedure and which usually results in the cessation of the bleeding, at least for the time being (Fig. 4).

FIG. 4

Diagnosis

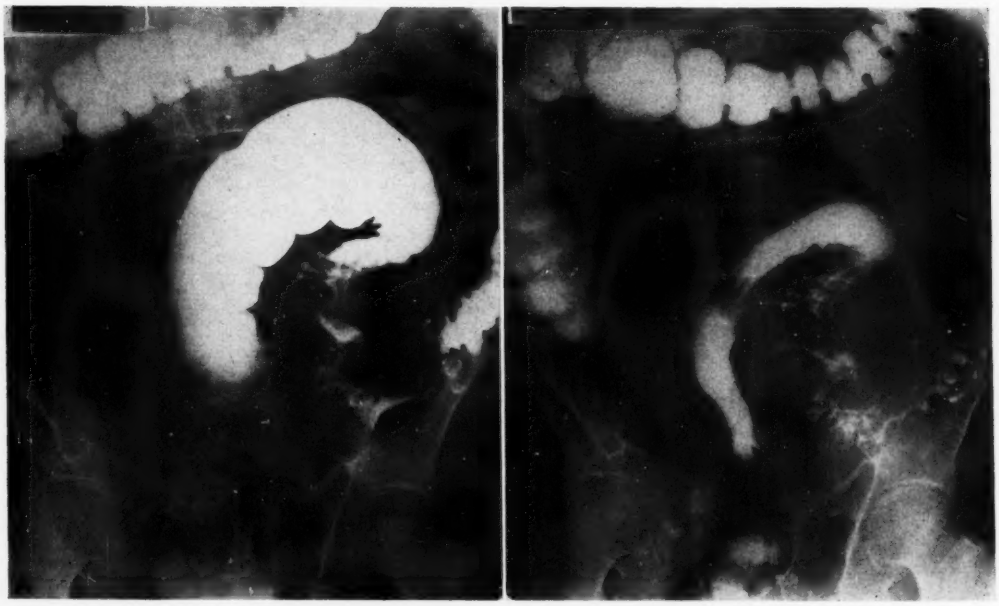
As pointed out by Schlicke and Logan,[3] "A report from the radiologist indicating the presence of diverticulosis of the sigmoid without diverticulitis does not mean that significant inflammatory changes are absent. This discrepancy should be recognized by all clinicians and is one of the pitfalls of blind belief in the infallibility of x-ray examination."

In further reference to roentgenologic diagnosis in uncomplicated cases of diverticulitis, the most difficult differential diagnosis involves carcinoma. In this regard Schatzki[4] stresses the following points:

(1) In diverticulosis a long segment of bowel is likely to be involved, while in carcinoma usually a short one is affected.

Chronic diverticulitis with complication of massive bleeding. A woman, aged 75, had sudden massive bleeding from rectum requiring 6 units of whole blood for adequate replacement. Laparotomy was then performed with finding of very extensive severe acute diverticulitis of the entire sigmoid plus lower descending colon. Bleeding ceased following completely diverting transverse colostomy. Barium enema evacuation film of left colon 2 weeks following colostomy shows innumerable diverticula. Extensive resection of left colon and closure of colostomy 4 months after initial operation resulted in recovery.

FIG. 5



Chronic diverticulitis with coexistent carcinoma. A man, aged 55, had chronic recurring pain in the L.L.Q. with x-ray findings (A and B) of diverticulitis with a filling defect in sigmoid. Carcinoma was not diagnosed preoperatively but was found during anterior resection of sigmoid. He recovered from the operation.

(2) In diverticulitis the mucosa is intact, but in carcinoma it is destroyed.

(3) A bizarre, fringed contour (picket-fence deformity) is more often associated with diverticulitis.

(4) Spasm of the colon is more constant in diverticulitis than in carcinoma.

(5) The presence of cone-shaped ends of the bowel outlined above and below the involved segment suggests diverticulitis (Fig. 5).

Summary

Among well-informed physicians there has been a definite swing in the past several years away from the conservative and toward the surgical treatment of diverticulitis of the colon, except in cases of mild or moderate degree and of fairly short duration.

This is due to a better appreciation of the severity of the complications, the increasing frequency of the disease in an aging population, and the relative safety of colon resections in the hands of surgeons accustomed to dealing with these problems.

Whereas formerly surgery was reserved for the treatment of the complications of diverticulitis resulting in protracted illness and multiple stage operations, we now with increasing frequency carry out primary resection and anastomosis for the still uncomplicated cases experiencing recurring fever, pain and mild obstruction. This approach to the problem has much to recommend it since it not only terminates morbidity and financial loss to the patient, but also protects him from the development of the truly dangerous complications of this disease.

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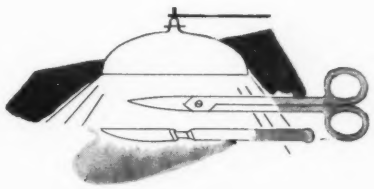

Postoperative Complications of Colon Surgery*

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HENRY FINCH, M.D.,† *Atlanta, Ga.*

When one looks back at the mortality rates which accompanied operations on the large bowel in the days before antimicrobial drugs were available, one becomes truly appreciative of the advances in medical science.

LEST WE FORGET—the chief problem which confronted the colon surgeon just three decades ago was peritonitis. This fact is best illustrated by an article published in the *Archives of Surgery*, January 1931, in which Bargen and Rankin[1] reported 222 patients operated on at the Mayo Clinic by "all forms of surgical maneuver that are applied to the colon" with 11 deaths from peritonitis. All of these received an intraperitoneal vaccine. Of another 58 cases operated on with "lesions of similar situation and nature" but receiving no vaccine, 13 died of peritonitis. Thus the over-all mortality from peritonitis was 8.5 per cent. Even though the introduction of the intraperitoneal vaccine seemed to be of some benefit, the problem of peritonitis forced the utilization of the extraperitoneal operation and the so-called aseptic anastomosis. Although better anesthesia, whole blood transfusions, attention to electrolyte balance and other surgical improvements have played a large part in reducing the over-all mortality; (and again, lest we forget—this over-all mortality was 18 to 20%[2]) the use of antibiotics must be given credit for reducing the incidence of peritonitis as well as other postoperative infections.

Because of side-effects of every antibiotic used so far and reported, there are those[3] who would discard all antibiotics and depend entirely on a good emptying of the colon before operation and careful surgical technic. This attitude, in our opinion, would simply turn the clock back. The importance of relieving obstruction and emptying the gut before bowel surgery was recognized and practiced 30 years ago. Also magnesium sulfate and castor oil were just as effective then as they are today.

Now the problem still undetermined is which antibiotic is the best for use in colon surgery. Much has been written about preoperative preparation of the colon, but as Dearing[4] states, "few clinical investigators have collected series of cases to determine the value of the postoperative use of antibiotics."

In 1952, we[5] reported the work done by the junior author on cases in which gross contamination of the peritoneal cavity had occurred, as in gunshot or stab wounds of the abdomen, and in which septic peritonitis did not develop after the use of chloramphenicol. We further reported on the use of chloramphenicol and dihydrostreptomycin (Chlorostrep) for preoperative preparation and postoperative medication in colon surgery.

Clinical Material and Evaluation

We wish to report a series of 161 laparotomies for colon surgery in which Chlorostrep was given 2 days preoperatively, then chloramphenicol intravenously for 3 to 4 days postoperatively, and after the patient could tolerate fluids and food by mouth, Chlorostrep was again given orally for some 3 or 4 days more. None of these patients were given penicillin or any combination of drugs with penicillin, nor did they receive any of the other broad spectrum antibiotics during this period. Preoperatively, however, practically all of these patients were given either phthalylsulfathiazole (Sulfathalidine) or succinylsulfathiazole (Sulfasuxidine) following the recommendations of Poth,[6,7] and some had the combination of Sulfathalidine and Neomycin.

*Read before the Section on Proctology, Southern Medical Association, Fifty-Fourth Annual Meeting, St. Louis, Mo., Oct. 31-Nov. 3, 1960.

This is not a record room survey of a group of cases but rather a review of the postoperative complications in a group of patients in whom the operation was done by and the follow-up care personally supervised by one or both of us.

This series includes 55 Miles' abdominoperineal resections; 2 Hartmann's procedure; 12 pull-through operations of the Babcock-Bacon type; 25 anterior resections; 24 complete or partial colectomies; 10 colostomies; 32 colotomies with polypectomy and colonoscopy; and one closure of a Devine colostomy with end-to-end anastomosis (Table 1).

All anastomoses were by the open method with the use of suction and direct approximation of tissues.

In this series there were 3 surgical deaths:—one cardiac death in a patient with hypertensive heart disease shortly after operation; one instance of pulmonary embolism occurring 7 days after operation; and one case of paralytic ileus and uremia 7 days after an abdominoperineal resection. The first 2 deaths occurred in patients we believed curable for cancer while the last occurred after a palliative procedure.

A resume of the postoperative complications include the following: There was one reaction to blood transfusion occurring while the patient was on the table and resulting in generalized urticaria, cloudy urine and anuria for several days. He recovered but died a year later from cancer.

There were 6 cases of postoperative obstruction, 2 of these occurring 8 months and 2 years respectively after the primary operation and both due to metastatic carcinoma. Three patients having mechanical obstruction had operations for the release of adhesions during the second week of convalescence. The sixth patient had postoperative obstruction 9 months following a pull-through procedure. The 4 patients having mechanical obstruction made an uneventful recovery and are alive.

TABLE 1

Abdominoperineal resections	57
"Pull-through" operations	12
Anterior resections	25
Colectomies, complete or partial	24
Colostomies	11
Colotomies with polypectomy and colonoscopy	32
Total number of cases	161

The 2 who had postoperative obstructions due to cancer did not survive.

In the 11 cases in which pull-through operations were done, 2 abscesses occurred in the presacral area. Figure 1 illustrates one case. Also, 2 other patients developed infection anteriorly and the abscess resulted in small rectovaginal fistulas. They have not been repaired as they are no larger than a match stem, and if enemas are taken daily they are producing no disturbing symptoms. While suction drainage of the presacral space for the first 48 hours postoperative through the original abdominal incision has reduced the incidence of occurrence of hematoma and abscess formation, the morbidity of the pull-through procedure has run above 20%, which is the experience of Black[8] at the Mayo Clinic.

Two patients having a low anterior resection developed hematoma and abscess: one drained through the suture line into the bowel and the other was aspirated through the vagina.

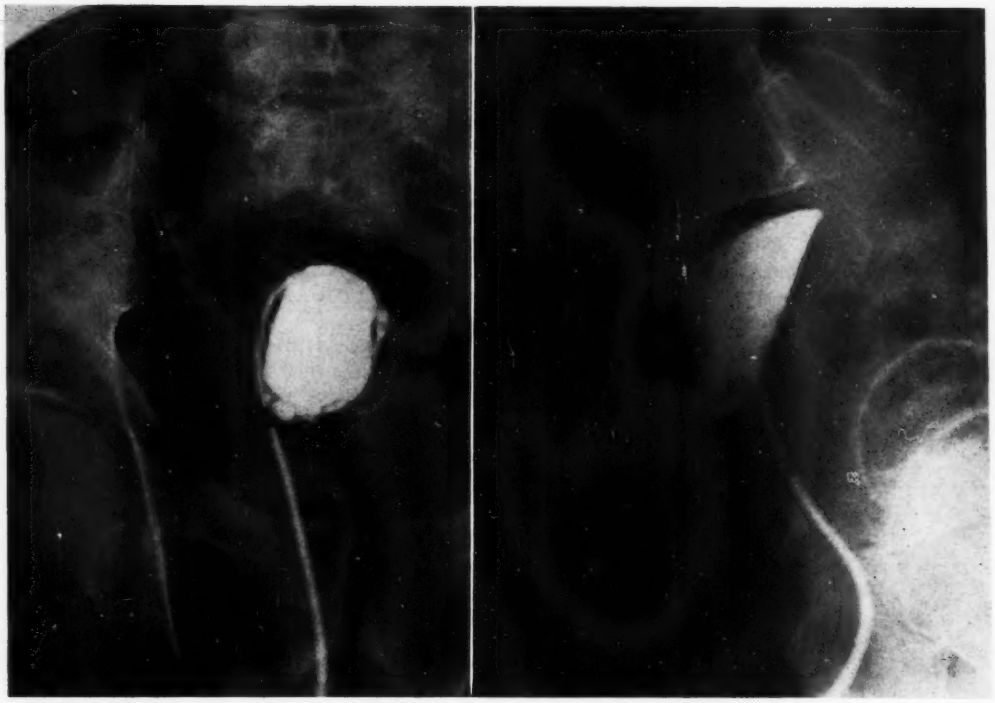
In addition to the abscesses already mentioned we have had 3 rather severe postoperative wound infections which finally healed but gave much concern. Two were in elderly patients and one was a diabetic. Laudable pus, however, in postoperative wounds was conspicuous by its absence.

Cystitis occurred not infrequently, usually following removal of the catheter 5 to 7 days postoperatively. Three transurethral resections were necessary to clear this condition. As the urinary infection was usually resistant to chloramphenicol at this time, sensitivity tests proved nitrofurantoin (Furadantin) to be the best drug available for treatment of the cystitis.

One wound disrupted and required resuture 9 days postoperative in an obese alcoholic patient who had coughing postoperatively.

There were no cases of postoperative pneumonia or pneumonitis. Nor were there instances of thrombophlebitis, even in the fatal case of pulmonary embolus. There were no cases of staphylococcal enterocolitis or evidence of staphylococcal infection elsewhere; nor were there instances of septic parotitis, a not infrequent complication in the past in patients having colon surgery. We have seen no evidence of depression of the hemopoietic sys-

FIG. 1



tem resulting in aplastic anemia or agranulocytosis. Finally, there were no deaths from peritonitis.

Comments

In 1951, Herrell[9] reported on the danger of using chloramphenicol because of its association with aplastic anemia, and advocated the use of tetracyclines instead. The anticipated incidence of association of aplastic anemia is probably less than 1:100,000 patients.[10] In 1958, Herrell[11] stated that half of the cases of aplastic anemia occurred in the age group under 12 years, and he still believed the drug to be indicated in typhoid fever and salmonellosis. Only one patient in our series was less than 12 years old and as this reduces the incidence by half, we believe the calculated risk involved is minimal and the use of the drug is justified.

Turnbull,[12] in 1956, reported 9 cases of staphylococcal enterocolitis in 51 cases of total colectomy for ulcerative colitis. He cautioned against the use of chlortetracycline hydrochloride and oxytetracycline because of this complication. In 1959, Turnbull[13] again reported the incidence of staphylococcal enterocolitis in approximately 5% of a reported series of cases in which Neomycin and Sulfathalidine were used preoperatively. We do not live in an isolated section where staphylococcal infections do not occur. In the Atlanta hospital where most of our patients were operated upon, staphylococcal infections have occurred and have been studied for control by the U. S. Public Health Service. Seven deaths were attributed to staphylococcal infection on the surgical service in a 14 month period. These included cases of staphylococcal pneumonia and staphylococcal enterocolitis.

It is not our purpose to convert anyone to the use of this antibiotic nor do we claim Chlorostrep to be the antibiotic ultimately to be accepted as the best choice by common usage. However, insofar as we are aware, ours is the largest series of cases so far reported in which chloramphenicol was used exclusively in colon surgery postoperatively. Rather than voicing opinions on drugs to be recommended or not recommended,[14] let us simply look at the record and let comparative reports fol-

lowing the use of different antibiotics speak for themselves.

Summary and Conclusions

1. This series of 161 laparotomies for colon surgery is presented with a review of the postoperative complications.

2. The authors believe that Chlorostrep (a combination of chloramphenicol and dihydrostreptomycin) and chloramphenicol have justified their use in the reduction of postoperative infections—particularly peritonitis.

3. This review is published for comparison with similar reports of antibiotics now in use, or new ones to be developed in the future. It is hoped that one antibiotic will some day be found which will eradicate infection without any unfortunate side-effects.

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Discussion (Abstract)

Dr. George H. Thiele, Kansas City, Mo. It is a pleasure to discuss this excellent paper and I wish to thank the authors for the opportunity to do so. I only wish that I could present figures comparable to the ones they have achieved by the use of chloramphenicol and dihydrostreptomycin in the prevention of complications following colon surgery.

We should keep in mind when we consider morbidity and mortality figures based on the use of any medication, that there are other factors which must also be considered. One of these has been mentioned in the authors' statement that staphylococcal infections have been epidemic in the Atlanta area. Another factor is the preoperative preparation of the patient's skin. Are careful scrubbing technics followed meticulously by us, our assistants and the surgical nurses? Are we sure of our rubber gloves? Are leaking gloves detected and changed at once? Recent investigations indicate that a definite percentage of brand new gloves will be found to have holes when examined electronically. All of these factors, as well as the use of antibiotics, enter into the morbidity and mortality encountered in colon surgery.

Since I cannot present statistics on the use of specific antibiotics pre- and postoperatively in as large a series as 160 cases, I thought it might be interesting to compare results in an equally large series, some of which were from the pre-sulfa and pre-antibiotic eras, with the results reported by Drs. Boling and Finch.

This series includes 160 cases chosen at random and covering a period from 1934 to 1960. The procedures are distributed as follows:

Miles' abdominoperineal resection	69
Colostomy	33
Anterior resection and anastomosis	20
Complete or partial colectomy	15
Hartmann's procedure	11
Colotomy and colonoscopy	7
Posterior resection	2
Mikulicz's resection	2
Ileostomy without resection	1
	160

Thirty-one cases were previous to 1943 when Sulfasuxidine (and later Sulfathalidine) became available. Thirty-seven cases antedated the use of penicillin postoperatively, and 58 antedated the postoperative use of Streptomycin in combination with penicillin. There are 31 cases in which Streptomycin was given in conjunction with Sulfathalidine preoperatively, and 66 cases in which Neomycin and Sulfathalidine were given in combination preoperatively. Thirty-five patients of the 66 patients were also given nystatin with the Neomycin-Sulfathalidine combination. Fifty-five of the 66 were given procaine penicillin G in combination with dihydrostreptomycin (Durycin) postoperatively.

Complications may be summarized as follows:

Peritonitis. In the series of 31 cases without pre- or postoperative sulfa or antibiotics, there were no deaths from any cause. Thirty-two patients were given Sulfathalidine preoperatively, and of these, 3 died, one of whom had penicillin postoperatively, and 2 of whom had a combination of penicillin and Streptomycin postoperatively. In 97 patients who had Sulfathalidine and either Streptomycin or Neomycin preoperatively, in conjunction with penicillin and dihydrostreptomycin, there were no deaths from peritonitis.

Wound Dehiscence. There were 9 instances of this, occurring at an average age of 60, and on an average on the ninth postoperative day. Eight of the 9 dehiscences occurred since the advent of preoperative antibiotic therapy. All had been fortified with glucose and vitamin C, and had normal or near-normal levels of serum protein. Five followed Miles' resections, 3 followed partial colectomies, and one followed a Hartmann's procedure.

Infected Incisions. There were 12 incisional infections, the only really severe one occurring in a badly

nourished man of 75 years who had a one stage colectomy because of ulcerative colitis. Three occurred in patients who had had no pre- or postoperative sulfa or antibiotic therapy, 3 in a series of 32 patients who had been prepared with Sulfathalidine alone, 3 in a series of 31 patients prepared with Sulfathalidine and Streptomycin, and 3 in 66 patients who were prepared with Sulfathalidine and Neomycin. Apparently the addition of Neomycin preoperatively reduced the incidence of wound infections by half.

Phlebitis. Two cases of only mild severity occurred.

Pulmonary Embolus. One fatal instance occurred on the tenth postoperative day.

Coronary Occlusion. There were 2 deaths in patients of 62 and 74 years.

Pneumonia. There were 2 deaths, one in the preantibiotic era, and one in August 1960. This man had Chlorostrep.

Transfusion Reaction. There was one fatal case in 1944.

Parotitis. None.

This series of 160 cases dating back to 1934 reveals a mortality of 9 deaths, 5.6 per cent. There were 3 deaths from peritonitis, a rate of 2%, all of which occurred in patients whose preoperative preparation consisted only of Sulfathalidine. The deaths from embolus, coronary disease and transfusion reaction cannot properly be related to chemical or antibiotic preparation or the lack of it.

I wish to congratulate Drs. Boling and Finch upon their paper. Surely their results would indicate that their management with the preoperative and postoperative administration of chloramphenicol and dihydrostreptomycin, is superior to the results I obtained with the various other preparations which were used in my series, all other factors being equal.

Dr. Boling (Closing). May I thank Dr. George Thiele for this review of his personal cases. As I have not studied his charts, seeing them for the first time with you today, I will make no comparison but will leave this entirely to each surgeon's interpretation. I would like to comment on the thorough reporting of the untoward effects of all antibiotics—be they of the anaphylactic shock type, superinfections—staphylococcal, or an association with aplastic anemia. The emphasis, however, is sometimes so great that we lose proper perspective and the picture may become out of focus. While the hazard of the drug may be one in thousands of cases treated, the reduction in mortality by its use may be several cases in every hundred.

By comparison, the reported fatality rate in the administration of general anesthesia is one in 10,800, and where muscle relaxants are also used, the death rate is one in 2,000 (*Lancet*, Oct. 30, 1954). In blood transfusions it is one in 1,200 (*A.M.A. News*, May 2, 1960).

We will continue to use chloramphenicol in colon surgery as long as our experience with it remains the same or until a superior antibiotic, proven by clinical experience, is found. However, if chloramphenicol were not available, we would use other antibiotics recommended rather than do without as we had to do, of necessity, in the past.

The Use of Gynecography in Pelvic Diagnosis*

HARRY M. LITTLE, JR., M.D., JOHN F. HUTCHINSON, M.D., L. E. RICHEY, M.D., and MELVIN SCHREIBER, M.D.,† *Galveston, Tex.*

Several methods for the visualization of the pelvic organs have been used over the past several decades with varying degrees of enthusiasm. The authors offer their experiences with this diagnostic approach.

GYNECOGRAPHY IS A TECHNIC that combines the use of two separate radiologic procedures. One procedure is hysterosalpingography; the other is pelvic pneumoroentgenography. The former is used frequently by gynecologists and general practitioners, but the latter is rarely used despite its proven value and safety.

In hysterosalpingography, a radiopaque substance is injected through the cervical canal into the uterine cavity and thence out the tubal lumens. X-ray studies taken during and after the procedure visualize the outline of the uterine cavity and tubal lumens.

In pelvic pneumoroentgenography, a gas is injected into the peritoneal cavity and allowed to collect in the pelvis. The gas acts as a contrast medium and x-ray films taken will show the pelvic structures outlined against this radiolucent background. The gas may be introduced by transuterine insufflation, cul-de-sac or transabdominal puncture.

Gynecography, the combination of the two procedures, will demonstrate on a single film both the status of the uterine cavity and tubal lumens and the contours and relative sizes of the pelvic structures. Gynecography gives the physician the maximum information that radiological procedures can provide about a woman's pelvic organs.

Uses

The primary use of hysterosalpingography is to demonstrate tubal obstruction or patency, tubal enlargements, congenital uterine abnormalities, and intra-uterine growths.

Pelvic pneumoroentgenography reveals changes in the size, contour, density, and location of the pelvic organs. The most common findings that can be demonstrated are: presence or absence of the normal pelvic organs, congenital abnormalities, uterine myomas, tubal enlargements, ovarian cysts and tumors, and adhesions. Occasionally, bladder and rectal abnormalities, and extension of tumor growths to the side walls of the pelvis can be visualized.

History

Irving Stein has done more to advance the use of pelvic pneumoroentgenography and gynecography than anyone. Since 1926, when he published his first work on pelvic pneumoroentgenography, Stein and his co-workers[2-5] have published many articles attesting to their great value in thousands of cases.

The first artificial pneumoperitoneum used for diagnostic aid was reported in 1902 when air was injected into the peritoneal cavity to help in visualization of the abdominal organs by endoscopy. By 1912 the use of pneumoperitoneum in conjunction with the x-ray for visualizing abdominal tumors was described. Hysterosalpingography was first reported by Cary,[6] in 1914, using collargol, a silver salt. In 1919, A. Stein and Stewart[1] first reported the use of oxygen pneumoperitoneum and x-ray for visualizing the pelvic structures. Rubin,[7] in 1921, reported the intra-uterine insufflation of oxygen as a test of tubal patency. Alvarez,[8] in 1921, introduced carbon dioxide as an intraperitoneal gas, and since then it and rapidly absorbed nitrous oxide have been used almost exclusively in

*Read before the Section on Gynecology, Southern Medical Association, Fifty-Fourth Annual Meeting, St. Louis, Mo., Oct. 31-Nov. 3, 1960.

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pelvic pneumoroentgenography and in the Rubin's tubal patency procedure. Also in 1921, Peterson[9] initially demonstrated the practical application of pelvic pneumoroentgenography as an aid in pelvic diagnosis.

In 1926, I. Stein[2] first reported his use and support of pelvic pneumoroentgenography. In 1927, he reported the combined use of hysterosalpingography and pelvic pneumoroentgenography, which he described as complete gynecography.[3] Decker in 1946[10] described cul-de-sac puncture as a means of performing the pneumoperitoneum. Numerous other authors[11-15] have, since 1926, written on the subject, reporting cases and noting modifications in technic and equipment.

Indications

Though gynecography is not indicated as a routine procedure in all gynecologic patients, there are many occasions where its use is valuable. Often its appropriate use will spare the patient a needless major surgical procedure; on other occasions the findings at gynecography will indicate the need for surgery. Stein feels that complete gynecography is indicated as a routine study in the sterility patient. Many gynecologists feel that hysterosalpingography alone is sufficient in these cases.

Pelvic pneumoroentgenography probably has a much wider use in gynecologic diagnosis than does hysterosalpingography. It can be of aid in just about any case where the routine methods of diagnosis have been insufficient or inconclusive. In addition to patients with sterility, pelvic pneumoroentgenography can be of great benefit in: the obese patient, the rigid uncooperative patient, children and others where only a rectal examination can be done; the patient suspected of having congenital abnormalities of the uterus, ovaries, or tubes; the patient suspected of having ovarian disease; and the patient who has had conflicting pelvic findings by the same or different examiners.

Contraindications

The contraindications to gynecography have been listed in the literature. Hysterosalpingography and transuterine insufflation are contraindicated in: pregnancy, uterine bleeding, purulent cervical or uterine discharge, acute or subacute pelvic inflammatory disease, shock, localized or diffuse peritonitis, large tumor masses filling the pelvis, and elderly patients or those who are poor risks from the cardiac viewpoint. The transabdominal route for pneumoperitoneum is said to be contraindicated in: shock; peritonitis; large tumor mass filling the pelvis; and, elderly or poor cardiac risk patients. Recently, competent investigators have questioned the validity of the latter three contraindications when used in selected patients.

Puncture through the cul-de-sac for pneumoperitoneum has the same contraindications as the transabdominal route and, in addition, it would not be indicated in any case where a free tap could not be anticipated or performed.

Complications

The complications of pneumoperitoneum in pelvic pneumoroentgenography are relatively mild and transitory. Nausea, vomiting, vertigo and abdominal pain are sometimes seen. Pain referred to the shoulder is not uncommon but is transitory and can usually be relieved by the patient assuming the recumbent position.

The most common complications of hysterosalpingography are more serious when they occur. Allergic reactions to the dye, venous intravasation of the dye with occasional pulmonary embolism, rupture of the uterus or tubes, and transportation of infection and/or tumor cells into the peritoneal cavity have all been reported. Fortunately, these complications are rare.

Technic

The technic of gynecography, or of its separate components, is relatively simple, requiring equipment that most physicians have access to, and which use minimal expenditure of the physician's time.

Different radiologists and gynecologists have developed their own preferred technics which will vary some with the one described below, but we have found the following method satisfactory for our use at the University of Texas Medical Branch Hospitals.

The patient's bowels and bladder should be empty. Often a small dose of an opiate or barbiturate about 30 minutes prior to the procedure is desirable. The pneumoperitoneum is performed with the patient on the x-ray table. The gas is injected by one of the three routes previously indicated. About

1,000 to 1,500 cc. of carbon dioxide are injected, using the Thomas Tubaflator* to indicate the volume of gas delivered and the pressure under which it is delivered (30 to 40 mm. of Hg.).

If the transabdominal route is chosen, puncture is usually made with an 18 gauge spinal needle below and to the left of the umbilicus after suitable preparation and anesthesia of the injection site.

If the transuterine route is chosen, the pneumoperitoneum is performed in almost the same manner as in the Rubin's tubal patency test—the only difference being the amount of gas injected and the pressure under which it is delivered. We have found that this route is more uncomfortable to the patient than the transabdominal route.

We have not used the cul-de-sac route for pneumoperitoneum but the technic of puncture would be the same as in culdocentesis, and the pressure under which the gas is delivered would be the same as in the other two routes of pneumoperitoneum.

As soon as the required amount of gas is delivered, the patient is placed in the prone position and the x-ray table tilted to 30 degrees of Trendelenburg position. The x-ray tube is angled 15 degrees toward the feet and positioned so that the central ray is centered over the tip of the coccyx. If complete gynecography is to be done, the desired radiopaque substance is then injected into the uterus through a previously placed intrauterine cannula.

A minimum of three exposures is routinely taken with the Bucky tray perpendicular to the long axis of the patient. One exposure is made using the calculated correct factors,** one is then overexposed, and the third underexposed. Since carbon dioxide is absorbed rapidly, we have found that by taking these three exposures immediately after pneumoperitoneum, at least one of the films will usually be of good diagnostic quality. Obliques and laterals are then taken as indicated.

Following this, the patient is kept under observation in the recumbent position for about 30 minutes. If she is in good condition and is an outpatient, she is then allowed to go home.

*Manufactured by Thomas Inst. Co., Houston, Texas,—Model #131

**Tube distance 36-40 inches

95-120 lb. patient 80-90 kvp	10-15 mas
120-170 lb. patient 90 kvp	25-30 mas
170-200 lb. patient 90-95 kvp	35-45 mas

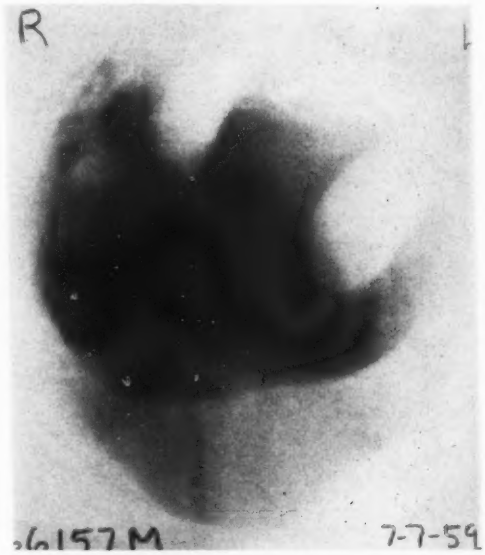
FIG. 1

(52377M) Pneumoroentgenogram showing large fibroid uterus with normal tubes and ovaries.

Results

At the University of Texas Medical Branch Hospitals, pelvic pneumoroentgenography and gynecography had been rarely used prior to 1957. Then three residents* of the Obstetrics

FIG. 2



(66157M) Pneumoroentgenogram showing normal sized uterus with bilateral ovarian enlargement.

*John F. Hutchinson, M.D., L. E. Richey, Jr., M.D., and Melvin Schreiber, M.D.

FIG. 3

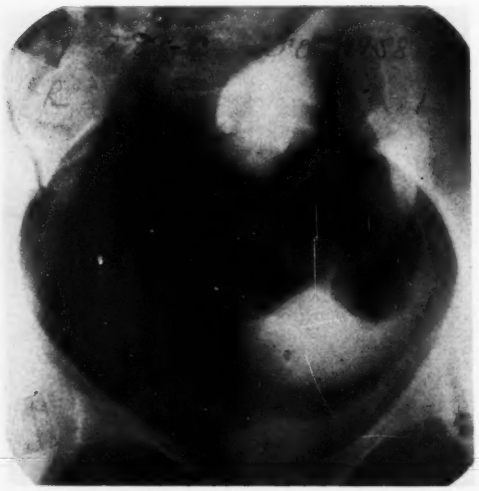
(57947M) Pneumoroentgenogram demonstrating bilaterally enlarged polycystic ovaries.

and Gynecology and Radiology Departments began using these procedures regularly on selected gynecologic patients. Since 1957 about 50 examinations of these types have been carried out, and in general the results have been satisfactory and a definite aid in pelvic diagnosis.

In a consecutive series of 40 patients reported on earlier this year,[15] the following results were obtained. Of 19 patients in this series who subsequently had other diagnostic and therapeutic procedures, 17 had had a correct diagnosis made at the time of gynecography or pelvic pneumoroentgenography.

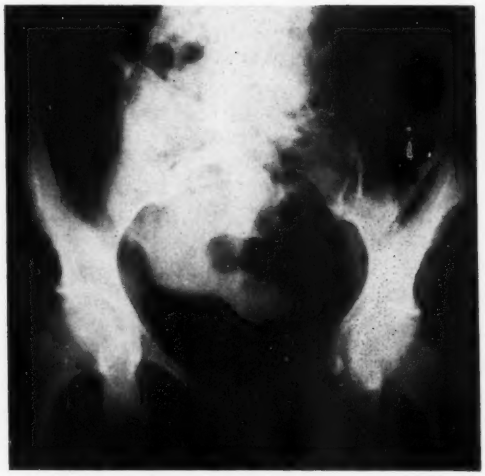
Seventeen patients in this series have as yet had no further diagnostic or therapeutic procedures performed, but in 9 it was believed that the information gained at the time of gynecography or pelvic pneumoroentgenography was sufficient to eliminate the

FIG. 4



(289C) Pneumoroentgenogram demonstrating thickened left adnexa adhesed to pelvic wall.

FIG. 5



(58934M) Pneumoroentgenogram showing large inflammatory cyst of right adnexa.

FIG. 6

(6750B) Pneumoroentgenogram shows an enlarged right tube, uterus of normal size, and left ovary slightly enlarged. Obesity made bimanual examination unsatisfactory.

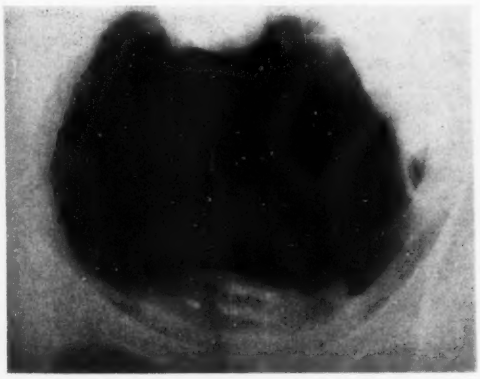
FIG. 7

(11060D) Pneumoroentgenogram of patient with large pelvic mass that proved to be uterus full of adenocarcinoma.

necessity of laparotomy, culdoscopy, culpotomy, or examination under anesthesia. The remainder of this group of patients are now either awaiting further studies or have been lost to follow-up.

The examinations were considered failures in 4 patients due to technical reasons: one, a patient with terminal pelvic malignancy, became ill after injection of a small amount of carbon dioxide, so the injection was stopped; the other 3 failures occurred early in the use of the procedures and were due to a major portion of the gas being injected retroperitoneally.

FIG. 8



(56855M) Pneumoroentgenogram of patient after total hysterectomy, bilateral salpingo-oophorectomy for adenocarcinoma of uterus. This shows pelvis free of masses.

FIG. 9

(8616H-A) Normal hysterosalpingogram with bilateral spillage. Faint outline of cystic pelvic mass can be seen.

The following cases in which gynecography and pelvic pneumoroentgenography x-rays were performed will show some of the various types of pathology that these procedures can demonstrate.

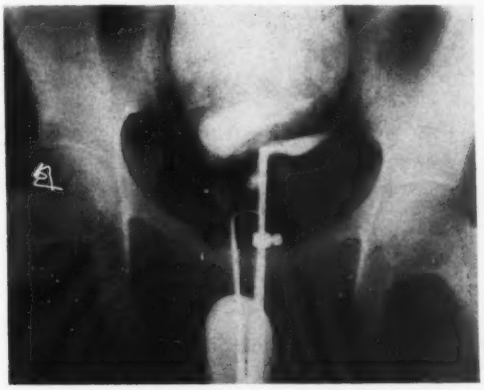
The *first patient* (52377M—Fig. 1) shows a large uterine fibroid. The ovaries and tubes appear normal.

The *second patient* (66157M—Fig. 2) reveals a normal uterus and tubes with bilaterally symmetrically enlarged ovaries. This patient was lost to follow-up before further studies could be done to substantiate a tentative diagnosis of Stein-Leventhal syndrome.

The *third patient* (57947M—Fig. 3) demonstrates a normal uterus and tubes with bilaterally enlarged ovaries in a patient with a diagnosis of Stein-Leventhal syndrome.

The *fourth patient* (289C—Fig. 4) shows chronic pelvic inflammatory disease with the left adnexa

FIG. 10



(8616H-B) Same patient as in figure 9 after pneumoperitoneum. Note large ovarian cyst covered with dye now clearly seen.

thickened and adhesed to the pelvic wall. The uterus seems slightly enlarged.

The *fifth patient* (58934M—Fig. 5) reveals a large inflammatory cyst of the right adnexa. At operation the right tube, ovary, and broad ligament were involved in this process. Several loops of ileum were adhesed to the superior surface of the cyst.

The *sixth patient* (6750B—Fig. 6) shows a right pyosalpinx, confirmed at autopsy 9 months later. (The patient died of complications of diabetes.)

The *seventh patient* (11060D—Fig. 7) demonstrates a large pelvic mass. In 1953, this woman received complete radiation treatment for a Stage II squamous cell carcinoma of the cervix. This mass was found at her subsequent yearly follow-up. The mass proved to be due to adenocarcinoma of the uterine fundus. She received further radiation therapy but died several months later of widespread metastases. At autopsy she was found also to have a carcinosarcoma of the uterus.

The *eighth patient* (56855M—Fig. 8) reveals the pelvic pneumoroentgenography of a woman who had had a total hysterectomy and bilateral salpingo-oophorectomy for adenocarcinoma of the uterus. Residual tumor was found in the vaginal cuff, but this x-ray study was interpreted as showing no pelvic tumor masses. Death in 1959 was due to widespread metastases, but at autopsy the pelvis was free of tumor.

The *ninth patient* (8616H-A—Fig. 9) demonstrates a normal hysterosalpingogram with bilateral spillage in a patient who was suspected of having Stein-Leventhal syndrome. The faint outline of a cystic pelvic mass can be seen.

The *final figure* (8616H-B—Fig. 10) shows the same patient after pneumoperitoneum was performed. A large left simple ovarian cyst, its surface covered with dye, can be clearly seen.

Conclusion

In conclusion, we have found gynecography and especially pelvic pneumoroentgenography to be safe, simple and valuable procedures. Though we are admittedly novices in their use, we have been satisfied with our results and can recommend these procedures as aids in pelvic diagnosis.

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Discussion (Abstract)

Dr. L. C. Powell, Jr., Galveston, Tex. The help offered in correct diagnosis by any procedure, such as gynecography, in selected cases makes it extremely worthwhile. As in every special diagnostic procedure its worth is limited, but our results have made us choose it more and more often in the obese, the uncooperative, the infertile or the very young patient. We have also found it very helpful in evaluating questionable masses lying against lateral pelvic wall in patients in our tumor clinic. Many times the fibrosis and stenosis which follow radiation therapy make adequate bimanual examination difficult to interpret.

Abrams and Hughes[11] reported a series of 161 cases. Their efficiency in making a definite diagnosis was about 75 to 80 per cent. As our experience has grown our own accuracy has improved. It is important to have the enthusiastic support of the radiologist, since it requires taking films with different technics to get readable or interpretable films in a given case.

Brown, Buice and Gould,[14] at the University of Arkansas, reported over 215 cases in late 1958. They have used this procedure even when large obvious masses are present to help determine preoperatively whether the lesions arise from uterus, ovary or bowel.

Several additional advantages can be put forth for this procedure in selected cases. The x-ray film provides a record available for other opinions, preoperative planning, and even for the medicolegal reasons, when and if they arise.

With the simplified technic, as described by the authors, gynecography should be more widely adopted and join the other special diagnostic procedures in use in gynecology, such as culdoscopy, culdocentesis and hysterosalpingogram.

I wish to re-emphasize that we are not advocating this procedure as a routine, but rather as an adjunct to diagnosis in selected patients.

A Correlation of the Gross and Microscopic Studies of Cancer of the Rectum in Relation to Operative Procedures*

WALTER A. FANSLER, M.D.,† *Minneapolis, Minn.*

All cancers of the rectum do not require radical treatment. Some are safely amenable to local excision. However, it needs experience and judgment in making the selection of such relatively benign lesions.

ALL AGREE that the majority of rectal cancers should be subjected to abdominal-perineal resection, anterior resection, or the "pull-through" type of operation. Experience has shown that one of these three radical operations will give the best chance of permanent cure in the case of sizable cancers. However, one should not be stampeded by the word cancer. Cancer is a disease of varying virulence, a fact that is too often overlooked. Every scratch on the hand does not call for amputation of the arm because of the fear of ascending infection, and neither does every rectal cancer call for abdominal-perineal resection. In the case of small lesions such procedure may be neither necessary nor advisable.

With a small lesion, if the clinical and microscopic findings are carefully evaluated, a few patients may be spared the inherent operative risk and postoperative sequelae of these major procedures with little or no loss of the chance of a permanent cure. I believe consideration of such a conservative approach in dealing with small lesions to be especially pertinent because of the fact that more and more rectal cancers are being discovered in their earlier, or more incipient stage. Small lesions may be removed just as completely by local excision as by more radical means. The only advantage of the radical approach is that if nearby metastatic nodes are present these are removed by radical surgery and this would not be the case if only local excision were done.

What size lesion may be considered a "small" cancer? In the case of a flat lesion, 1.5 centimeters is near the maximum diameter which should be considered "small." In the case of a polypoid lesion it may be somewhat larger for, in general, pedunculated tumors are more likely to be of a low grade of malignancy with less tendency to early invasion or formation of metastases. Flat lesions which are freely movable with the mucosa are suitable for local removal. Biopsy has shown some flat lesions, only 2 or 3 millimeters in diameter, to be adenocarcinoma histologically. Since such lesions are usually fulgurated without biopsy the percentage which are carcinomas is not known. In any event, no recurrence or metastatic spread has been reported following the fulguration of such tumors and so this treatment suffices. Flat tumors which are fixed to the underlying structures are less suitable for local removal. It has been noted that small flat tumors, with an ulcerated center and a rolled edge are more likely to be fixed and are usually of a higher grade of malignancy. Polypoid tumors with a long, well-developed pedicle are usually suitable for local removal. Those which have a short, thick pedicle or are sessile are less so. Pedunculated tumors 1.5 centimeters or greater are more likely to show malignant change than smaller ones.

If, after gross examination of the tumor, the surgeon considers it for possible local removal, the next step should be the removal

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†Emeritus Professor of Surgery, University of Minnesota, Minneapolis, Minn.

of the entire tumor for examination by the pathologist. Biopsy of the tumor is not sufficient since the entire tumor may not be cancerous, and the cancerous portion may be missed by simple biopsy. Equally important, a partial biopsy does not show the extent of invasion and may not show the degree of anaplasia. Both of these factors are quite important in making a final decision. Flat tumors should be removed with a portion of the underlying bowel wall. The defect is then closed with a few interrupted chromic sutures. Tumors with a long pedicle may be removed by dividing the pedicle at its base. With short, meaty pedicles a portion of the bowel wall should also be included. Such a procedure carries no greater risk than an ordinary biopsy.

Consideration may now be given to the histologic findings. What findings justify the diagnosis of cancer? In some instances a tumor, which consists largely of adenomatous tissue but whose surface shows areas of cells with a loss of nuclear polarity, hyperchromatism, irregular cell outline, and more than one layer of nuclei not lined up in regular lines but showing no break through the basement membrane, is termed *carcinoma,* Grade I. I think the term *actively growing polyp with cancerous potentialities* would be a better term. Regardless of terminology, this tumor is nonmetastatic at this stage of development and local removal will produce 100% of cures. The word cancer is a frightening one to the patient, and unfortunately some surgeons, alarmed by the word cancer, do radical operations for this tumor when such a procedure is totally unnecessary. It should be repeated that the only advantage of radical operation over local removal is the possible presence of local metastases in the nearby fat which would not be removed by local excision.

The final decision as to the necessity of more radical surgery should be determined by the extent of invasion and the degree of anaplasia.

At present there are no statistics as to the percentage of metastatic spread from true cancers of the size under discussion. Dukes[1,2] reports his observations of metastatic spread based upon the extent of invasion of the tumor. No consideration is given to the size of the tumor or to the degree of anaplasia. The first group he described has invaded only the mucosa and these showed no metastases. The second group included tumors which had invaded the muscularis but he also included those which had completely penetrated the muscular coat and had locally invaded the perirectal fat. I believe a further subdivision would be far more helpful. The first should be limited to well-differentiated tumors which had invaded only the muscular coats of the bowel. The second should be limited to those tumors which had penetrated entirely through the bowel wall and invaded the adjacent fat. In the case of tumors graded I and II, according to anaplasia and which had not penetrated completely through the bowel wall, I doubt if the metastatic spread would be greater than the inherent mortality rate which must be accepted in doing a radical operation for rectal carcinoma. As to anaplasia Dukes[1,2] again classifies this group on the basis of the degree of anaplasia into three groups: I, II, or III (low grade, medium or high). Attempts have been made to further subdivide these grades, but I believe such attempts serve no useful purpose and only add to the confusion. Briefly stated, in Grade I tumors the cells have a minimal departure from normal and there is rather definite glandular formation. Grade II shows a greater cellular anaplasia and a less degree of glandular formation. In Grade III there are clumps of atypical, actively growing cells with little or no tendency to glandular formation.

In conclusion, what tumors are suitable for local removal? The tumors I have described, sometimes being diagnosed as Grade I carcinoma, or superficial carcinoma in a polyp, should always be removed locally. These are nonmetastatic lesions. Cancers, flat or otherwise, which show no invasion other than the mucosa and anaplasia of Grade I or II, may be removed locally in most instances. Flat cancers not more than 1.5 centimeters in diameter, which have partially invaded the muscularis but which have not penetrated through it, may be considered for local removal if the anaplastic grading is I or possibly II. In making a final decision to remove the tumor locally the surgeon must balance in his own mind the risk of local metastases being present against the mortality rate and postoperative sequelae of the more radical operation.

Of the last 100 cases of cancer of the rectum

operated upon by our group, only 3 were considered favorable for local removal. It is hoped that this percentage may be increased by the increasingly earlier detection of rectal cancers. Throughout the years I have had occasion, for various reasons, to remove rectal cancers locally with a surprising number of cures. I have also operated upon many small cancers by radical procedure because I feared to do less, only to find that in many no metastic nodes were present and a less radical procedure would have sufficed.

Two observations will be necessary to give any reliable statistics. First is the careful search for metastases after radical removal of small tumors in a large number of patients. Second is the observation for recurrence in an equal number of patients who have had local removal. Even this will not give an answer with slide rule accuracy, since cancer is an unpredictable disease. Small tumors may occasionally show metastases while also occasionally large tumors may not do so. I do believe the observations considered in this paper to be a guide to the avoidance of radical surgery in a limited number of cases. This decision, however, must rest upon the experience and surgical philosophy of the individual surgeon.

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Discussion (Abstract)

Dr. Patrick H. Hanley, New Orleans, La. I thoroughly enjoyed Dr. Fansler's paper, a presentation that I hope will help us to correlate the gross with the microscopic pathologic studies and thus prevent unnecessary radical operation in some patients. Because of his vast experience and his ability with clinical endoscopy, he selected only 3 cases of malignant tumors of the rectum for conservative removal. This indicates close and harmonious relationship with his pathologist, for without this cooperation such a program would be difficult. Too, unfortunately, inexperience with endoscopic evaluation of neoplastic lesions leads the endoscopist to accept all tissue reports from the pathologist without reservation, with the consequence that radical surgery is sometimes employed unnecessarily. One of the most frequent errors of this type I have observed on 3 occasions, is performance of abdominoperineal resection because of a histopathologic diagnosis of adenocarcinoma from biopsy of a small lesion. The surgeon thus proceeding does an abdomino-perineal resection only to find that after postoperative re-evaluation of the biopsy specimen and the completely removed tumor the diagnosis is reversed to carcinoid of the rectum, and he has a patient with an unnecessary abdominal colostomy. We as clinicians must be able to correlate the gross with the microscopic; frequent consultation with the pathologist and review with him of the microscopic evaluation will often make it easier to determine the most appropriate operative procedure. I thoroughly agree with Dr. Fansler that carcinoma, Grade I, should not be used. Instead, this should be designated actively growing polyp with cancerous potentialities, as Dr. Fansler calls it, or with slight or marked atypism as we do. Dr. Fansler has brought out that in clinical evaluation of carcinoma one is confronted with the ulcerated, sessile and polypoid type of neoplasm.

I would certainly favor, as Dr. Fansler does, local excision of pedunculated tumors with carcinomatous changes in the polyp if there is no frank invasion. In sessile lesions, as in the villous tumor, biopsy reports from pathologists may contradict one's clinical impression if the entire tumor is not removed, and one's clinical judgment then has to be relied upon, for the surgeon is responsible for the final decision. An example of this is this case of a benign villous tumor; attempt at removal through the transanal approach was impossible, and at this time other biopsy specimens were taken and invasive carcinoma was reported. Because this tumor was readily palpable and no areas of induration were felt, it was the clinical impression that this 6 by 9 centimeter villous tumor was benign. The patient outrightly refused to submit to the sure method of cure, a pull-through procedure. He was treated by repeated coagulation with multiple biopsies before each treatment; at no time was there any evidence of a carcinoma. The tumor was completely removed and the patient has remained well up to now.

In small, sessile neoplasms one's clinical evaluation is more likely to be accurate if conservative removal is decided upon. However, because of personal experience with small ulcerated lesions I am afraid that one cannot evaluate the true degree of malignant degeneration by the size. Dr. Fansler states that a cancerous disease of varying virulence, and by the same token, the degree of malignant degeneration or distant spread, cannot be determined by the size of the neoplasm. Small lesions may have distant metastasis either by the lymph or blood channels.

In October 1952, I operated on a white woman for a small ulcerated carcinoma of the rectum that measured 0.9 by 0.4 cm. One of 13 lymph nodes contained metastatic disease. Interestingly enough, this patient enjoyed good health for 7 years, at which time she was again operated on by Dr. John Ray because of a hernia about the colostomy; abdominal exploration further revealed one large solitary metastatic growth in the liver approximately 4 inches in diameter. This patient has subsequently died.

I saw a second patient 2 weeks ago, in consultation with Dr. Jeff Harris. The patient had a small, shallow, 1 cm. ulcer of the posterior part of the rectum. Abdominoperineal resection was performed and examination of the lymph nodes showed one to contain metastases. This experience has definitely shown that it is extremely difficult to evaluate clinically ulcerated lesions for local excision. However, I am sure that Dr. Fansler has seen such cases and his decision for abdominoperineal resection would have

been made on the basis of his clinical evaluation.

I thoroughly enjoyed this presentation and the emphasis on better clinical and histologic correlation in all lesions of the rectum, for there is nothing more depressing than to do a radical cancer operation and have the pathologist report no residual tumor.

I wish to thank Dr. Fansler for asking me to discuss this paper.

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The Problem of Hyperbilirubinemia*

VICTOR C. VAUGHAN III, M.D.,† *Augusta, Ga.*

What does icterus mean in the newborn? Is it of serious import; must exchange transfusions be done? These are difficult questions to resolve at times. This paper is an excellent one for reference.

HYPERBILIRUBINEMIA in the newborn infant may occur as an expected development in the course of hemolytic disease due to Rh incompatibility or as the unanticipated result of isoimmunization with respect to other blood group factors (such as A, B, Kell, or others), from infection, from the action of drugs, or from an intensification, without qualitative alteration, of the condition generally given the designation *icterus neonatorum*. In the newborn period threshold values for the level of bilirubin exist above which bilirubin is toxic to cerebral tissues. The resulting staining of the nuclear masses of the brain and the clinical features associated with kernicterus are well known. The infants with bilirubin encephalopathy who do not die in the newborn period have rather characteristic motor and usually intellectual disability in later life, often with impairment of hearing. In the light of the importance of hyperbilirubinemia as a signal of danger to the infant, the physician who addresses himself to the problem of the jaundiced newborn infant must be aware of the large number of factors governing the economy of bilirubin in the newborn period.

When the destruction of red blood cells leads to the elaboration of bilirubin, this first appears in the blood in a form giving the indirect van den Bergh reaction and associated with the albumin fraction of plasma protein. The process of excretion of bilirubin by the liver involves the conjugation of the indirect-reacting bilirubin with glucuronic acid to form a soluble bilirubin glucuronide. Icterus neonatorum has been shown to be consequent at least in part upon a deficiency of activity of an enzyme (glucuronyl transferase), which effects the union of the bilirubin and glucuronic acid molecules. In the normal full-term infant this deficiency begins to be corrected by the third or fourth day, so the hyperbilirubinemia of icterus neonatorum shows a peak on the third, fourth or fifth day, with rapid correction thereafter. The duration of the enzyme deficiency is somewhat prolonged in premature infants, who may reach their peak levels of bilirubinemia on the fifth or sixth day of life. The levels reached in the absence of factors contributing to unusual degrees of hyperbilirubinemia do not generally exceed 10 to 12 milligrams per 100 ml. in full-term infants nor 15 milligrams per 100 ml. in premature infants. In both groups, however, the level may sometimes exceed 20 milligrams per 100 ml., which is generally taken to be the point at which anxiety for the possibility of kernicterus begins to be felt.

Many estimates have been given as to how frequently clinical icterus occurs in the newborn infant, with a wide range of frequencies reported. This problem was studied some years ago by Dr. F. Brelian and myself[1] in a nursery where daily careful observation was made of more than 800 infants on each of the first 5 days of life. We found that icterus neonatorum made its appearance some time during this period in 35% of white infants and 13% of negro infants (Table 1). Icterus neonatorum was more commonly observed in white male infants (40%) than in white female infants (31%); the difference appears statistically significant (chi-square is 4.2, 1 d.f.). No sex difference was observed for negro infants. Among

TABLE 1

RELATION OF SEX AND RACE TO INCIDENCE OF ICTERUS NEONATORUM IN 875 NEWBORN INFANTS

	Male	*Female*
White (413)	40%	31%
Negro (462)	12%	13%

Differences noted are statistically significant (p less than 0.05) except for the sex difference in negro infants (see text).

*Chairman's Address, read before the Section on Pediatrics, Southern Medical Association, Fifty-Fourth Annual Meeting, St. Louis, Mo., Oct. 31-Nov. 3, 1960.

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these more than 800 full-term infants no important relationship was seen between birth weight and either the frequency of occurrence or the maximal intensity of icterus (Table 2). It has been well established, however, by other studies that the frequency of clinical icterus neonatorum is notably increased in premature infants.

The work of Halbrecht[2] and of others has drawn attention to the fact that when conspicuous icterus is seen on the first day of life, it is almost always a sign of hemolytic disease of the newborn due to Rh or A or B incompatibility. We were surprised, therefore, to find that in about 10% of those white and negro infants in whom icterus was seen within the first 5 days of life it had its onset within the first 24 hours after birth (Table 3). The majority of these infants had no evidence of hemolytic disease of any known origin, and in the majority of them the maximal intensity observed *on the first day* was faint only. On the other hand, in 5 of the 9 infants in whom icterus noted on the first day reached *moderate* intensity, blood group incompatibility was demonstrated as a probable contributing factor. Evidently, we must emphasize that it is *conspicuous* icterus within the first day of life that carries a high likelihood of hemolytic disease due to blood group incompatibility. When jaundice of obscure origin remains mild in degree and the bilirubin level low, impetuous use of exchange transfusion in anticipation or prophylaxis of as yet unestablished hyperbilirubinemia is uncalled for, even when A or B blood group incompatibility can be demonstrated.

It was in the course of an investigation undertaken to establish how often incompatibility of mother and infant, with respect to A or B, might be responsible for clinical icterus in infants who would not have become jaundiced except for this incompatibility that we came to know that substantial numbers of infants with faint icterus on the first day of life do *not* have hemolytic disease. In these studies,

TABLE 2

RELATION OF OCCURRENCE OF ICTERUS NEONATORUM TO BIRTH WEIGHT

Birth Weight	*White* *Per Cent Icteric*	*Negro* *Per Cent Icteric*
Under 6 lbs.	35% of 51	13% of 103
6-7 lbs.	37% of 118	16% of 163
7-8 lbs.	35% of 139	15% of 142
Over 8 lbs.	33% of 33	9% of 65

TABLE 3

TIME OF ONSET OF ICTERUS NEONATORUM IN JAUNDICED INFANTS

Day of Onset	*White*	*Negro*
1st	10%	10%
2nd	33%	25%
3rd	37%	43%
4th	12%	19%
5th	8%	3%

because Rosenfield[3] had shown that hemolytic disease due to A or B iso-immunization is found almost exclusively in the A or B infants of group O mothers rather than in the incompatible infants of A or B mothers, we gave particular attention to the relationship of the occurrence and intensity of icterus neonatorum to incompatibility with respect to A or B in infants of mothers of group O. Table 4 shows that in the group of infants studied there was a significant excess of jaundiced infants in the incompatible offspring of negro mothers of group O, which can be estimated to amount to about one fifth of icteric negro infants or to about 3% of all negro infants observed during the time of this study. Incompatible infants of A or B mothers displayed no such excess incidence of icterus neonatorum, nor was any excess frequency of icterus seen in incompatible white infants of O mothers. These results indicate that while most icterus neonatorum in negro infants is not related to blood group incompatibility, the occurrence of neonatal icterus will more commonly, in the negro infant than in the white infant, serve as a warning that hemolytic disease may be present with its potentialities for marked hyperbilirubinemia.

Icterus neonatorum is evidently a poor index for hemolytic disease due to incompatibility in the major blood groups in the white infant, owing presumably in large part to the much increased incidence of benign icterus in these infants. It is of passing interest, on the other hand, that as many as 3% of all infants may have, with or without icterus, a mild or subclinical form of hemolytic disease of the newborn due to A or B incompatibility. This can be inferred from the result of the determination of the spontaneous agglutinability of the cells of the infant in a colloidal medium such as a solution of glue or of acacia. In the group of infants referred to above, in 321 instances where the compatibility of mother and infant was known, agglutinability in colloidal media selected to a high degree (chi-square greater

TABLE 4

RELATION TO A OR B INCOMPATIBILITY

Maximal Icterus	Group O Mothers		Other Mothers	
	Incompatible	*Compatible*	*Incompatible*	*Compatible*
Neonatal Icterus in White Infants				
None	15	20	6	38
Faint	0	7	2	7
Moderate	8 } 48%	9 } 32%	0	16 } 37%
Marked	6	3	0	10
Neonatal Icterus in Negro Infants				
None	32	88	19	93
Faint	5	6	1	2
Moderate	8 } 23%	9 } 9%	4	15 } 14%
Marked	3	0	0	0

The observed bias toward increased icterus in incompatible white infants of group O mothers would need to be sustained in a group of infants nearly twice as large in order to obtain statistical significance at p less than 0.05.

than 20, P less than 0.001) a group of infants who were incompatible with their mothers (Table 5). The frequency of positive tests in incompatible infants was 16%, in compatible infants, 3 per cent. No racial differences were noted. It can be estimated that a positive reaction in this system represents A or B incompatibility about half the time, and that the frequency of "hemolytic disease" inferred from this test is about 3% of all infants.

It appears, then, that blood group incompatibility with respect to A or B which does not lead to hemolytic disease of the newborn of such intensity as to call for diagnostic and possible therapeutic activity contributes in only a small way to icterus neonatorum. Furthermore, in at least 2 out of every 3 instances in which hemolytic disease of the newborn due to A or B incompatibility might be presumed from an abnormality in the red cell or from appearance of icterus, the clinical course will be entirely benign, either without icterus or with undifferentiated "icterus neonatorum." There may or may not be mild spherocytosis, reticulocytosis, or other indices of hemolytic susceptibility or activity.

The determinants of icterus neonatorum just discussed may be designated as uncontrolled or "normal": i.e., race, sex, level of maturity, and "subclinical" A or B blood group incompatibility. There are other contributing factors more clearly related to unusual or abnormal conditions. For example, Miller[4] has called attention to an increased intensity of subsequent hyperbilirubinemia in infants with presumptive anoxia at birth. Bacterial or other infection, such as cytomegalic inclusion disease, toxoplasmosis, or syphilis, commonly leads to jaundice, as may rare hemolytic syndromes such as acquired hemolytic anemia, hereditary spherocytosis, or certain nonspherocytic hemolytic processes. Among the latter are the congenital hemolytic syndrome which Zinkham[5] has shown to be related to genetic absence of glucose-6-phosphate dehydrogenase and the possibly closely related hemolytic process produced by administration of large doses of water-soluble analog of vitamin K to the infant or to the mother prior to delivery. This last, it has been shown,[6] may be responsible for raising an otherwise harmless level of bilirubin beyond a damaging or lethal threshold. It is urgent that the use of vitamin K and other drugs, such as sulfonamides or sedatives or analgesic agents, either for the mother in labor or the infant following birth, be thoughtfully and deliberately and carefully planned, and that new agents be critically evaluated as to their safety for the infant from the standpoint of bilirubin economy. The recommended prophylactic dose of vitamin K has been set at one milligram. The list of drugs having the same or a similar effect is incomplete, but probably includes certain sulfonamides, and may prove to contain other new drugs increasingly commonly used as anal-

TABLE 5

SPONTANEOUS AGGLUTINABILITY OF INFANT'S CELLS IN COLLOIDAL MEDIA

Infant	*Positive Agglutination Tests* White	Negro
Compatible	4 of 74 (6%)	2 of 154 (1%)
Incompatible	6 of 29 (20%)	9 of 62 (14%)

Differences favoring agglutinability of incompatible cells are highly significant (p less than 0.01).

gesic or sedative agents. Further study of this phenomenon is underway.

Though unrelated to the production of hyperbilirubinemia, it is of enormous importance to the infant with an established high level of serum bilirubin that there is instability in the complex formed between indirect bilirubin and serum albumin. The nature of this instability is such that when certain sulfonamides or certain other drugs are given to the infant, the indirect bilirubin may be displaced from its attachment to albumin. When this detachment occurs, bilirubin appears to move readily out of the vascular compartment into cerebral and possibly other tissues where it has its most toxic effects. The dangerous effects of sulfisoxazole in the icteric newborn infant were first demonstrated by Silverman and his coworkers,[7] and the list of drugs capable of displacing bilirubin has been extended by Odell[8] and others to include other sulfonamides, salicylates, caffeine sodium benzoate, hematin, glucuronic acid, certain lipids, and possibly heparin (through a secondary effect upon serum lipids). The bilirubin-albumin complex appears to be less stable at a relatively low pH than at normal pH of blood. It is noteworthy that when bilirubin is released from its attachment to albumin through the mediation of any one of the above agents, the serum level may fall rapidly as bilirubin leaves the vascular compartment; kernicterus may have its clinical onset as the falling level becomes apparent.

It is against the above background descriptive of icterus neonatorum and of conditions modifying or controlling the level of serum bilirubin that we must seek adequate measures for the study and control of hyperbilirubinemia. The most important icterogenic condition in the newborn is frank hemolytic disease of immune origin due to incompatibility with respect to the Rh factor or to A or B or other blood group factors. *Hemolytic disease* will serve as the most useful prototype in consideration of the manifold factors governing clinical management of hyperbilirubinemia.

The aspects of hemolytic disease of the newborn which have a high degree of correlation with the likelihood of hyperbilirubinemia include, in addition to those factors such as prematurity which dispose to hyperbilirubinemia in all newborn infants: history of outcome in previously affected children, level of maternal antibody (only, as a rule, in the case of Rh incompatibility and with limitations), the general clinical condition of the infant at birth, the level of hemoglobin in cord blood, the level of bilirubin in cord blood, and changes in the level of serum bilirubin subsequent to the determination in cord blood.

Prior to the time of delivery of the infant with hemolytic disease of the newborn his probable need for vigorous treatment directed at the prevention or control of hyperbilirubinemia can often be only a little better than vaguely surmised. A history of a previous infant severely affected, particularly if such an infant has suffered from kernicterus, carries a relatively high risk of severe hyperbilirubinemia in a subsequent infant, but a less severely affected infant may follow. Statistical studies indicate broad correlations of likelihood of illness in the infant with maternal titer during pregnancy, but in the individual instance exceptions to expectation at both ends of the range of titer in the sensitized mother are so common as to render this a weak index to the probable need of the infant for treatment.

The presence at birth of hepatosplenomegaly, pallor, or edema may give evidence of an active hemolytic process in the infant, and in infants with no clinical evidence of such a process there may often be laboratory evidence thereof, such as a hemoglobin level below 14 to 15 grams per 100 ml. in cord blood, or a bilirubin level in cord blood in excess of 3.5 to 4.0 milligrams per 100 ml. Normoblastemia or reticulocytosis may give additional information. In any case, however, while conspicuous evidence of a hemolytic process indicates a substantial likelihood of blood destruction to follow, some infants handle the excess burden of active hemolysis surprisingly well so far as hyperbilirubinemia is concerned. Until the capacity of the individual infant to excrete bilirubin becomes evident, it is the initial or changing level of serum bilirubin itself which constitutes the best index of probable danger. Levels of bilirubin in cord blood above 5 or 6 milligrams per 100 ml. indicate confidently that dangerous levels are to be expected, even before clinical icterus makes its appearance, and serial observations of the level of serum bilirubin may even more accurately predict dangerous levels long before they occur. For example, during the first few hours or first day of life, a rate of rise as high as or in excess of 0.5 milligrams per cent per hour predicts a

level in excess of 20 milligrams per 100 ml. within 48 hours. More rapid rises will exceed 20 milligrams per cent more quickly. The degree or time of onset of clinical icterus may be at times totally misleading as to danger of hyperbilirubinemia. Even when his serum may contain levels of bilirubin as high as 8 to 10 milligrams per 100 ml., the infant with hemolytic disease of the newborn is almost never jaundiced at the moment of birth; such infants generally become jaundiced within a few minutes or hours. The level of clinical icterus may appear to lag many hours behind a rapidly rising level of bilirubin in the first day or two. Occasionally, even in infants in whom hyperbilirubinemia of lethal intensity will occur, the apparent rate of early rise in bilirubin is slow, and the onset of clinical icterus may be delayed up to 48 hours.

The presence or intensity of a positive Coombs' reaction in the case of the infant with hemolytic disease due to Rh incompatibility gives no important indication as to the likelihood of hyperbilirubinemia. With proper technic a strongly positive Coombs' reaction is to be *expected* in the Rh-positive infant of a sensitized mother. In many such infants, particularly when the level of antibody in the mother is at low levels, the strongly positive Coombs' test will be associated with no clinical illness nor with any need for therapy. On the other hand, we have seen kernicterus in a number of infants in whom the Coombs' test was reported as negative, sometimes through laboratory error, sometimes apparently authentically. The Coombs' reaction must be determined in certain instances, however, since an apparently Rh-negative infant of a sensitized mother must, if the Coombs' test is positive, be presumed to be in fact Rh-positive with coated ("blocked") cells until and unless some other adequate explanation for his positive reaction is found.

It deserves once again to be emphatically stated that changes in the level of hemoglobin in the hours and days following delivery of the infant with hemolytic disease bear no useful correlation with the likelihood of dangerous levels of hyperbilirubinemia being encountered. Owing to redistribution of body fluids in the hours following delivery, there may actually be rises in the level of hemoglobin which may for as long as a day or two mask the orderly fall in hemoglobin level which is characteristic of the hemolytic process in these infants. In general, it may be stated that if the level of hemoglobin remains above 8 to 10 grams per 100 ml., the infant is in no immediate danger from anemia.

Serious concern for the possibility of kernicterus begins to be felt when the level of serum bilirubin reaches or exceeds 20 milligrams per 100 ml., but no accurate estimates can be made at the present time of the risk of occurrence of kernicterus at any given level in a particular infant. There is some evidence that the premature infant may, at any given level of bilirubin in excess of perhaps 15 milligrams per 100 ml., be more susceptible to kernicterus than the full-term infant, presumably owing to greater permeability of the blood-brain barrier. As the maturity of the blood-brain barrier advances, older infants are probably less susceptible than younger. We have not yet personally observed kernicterus with its onset after 120 hours of age in either the full-term or premature infant, but in premature infants with rising levels after this time kernicterus may well occur, and it is entirely probable that there is no age of man in which a sufficiently high level of indirect bilirubin may not lead to kernicterus.

This brief consideration of the circumstances under which hyperbilirubinemia can be expected to prove a threat in hemolytic disease emphasizes that kernicterus due to hyperbilirubinemia is the principal threat to recovery of the affected liveborn infant. Furthermore, hyperbilirubinemia can be adequately evaluated or studied only through direct knowledge of the bilirubin level in serum, and not by inference from other data. Wherever hyperbilirubinemia occurs the same principle applies. It is not always easy to know the level of bilirubin with precision or confidence. In hospitals where this is not possible and this deficiency cannot be immediately remedied, it is improper that the management of hyperbilirubinemia be undertaken. Fortunately, micromethods for bilirubin determinations are becoming more satisfactory, particularly with the use of "synthetic serum" standards, and we may expect the deficiencies and uncertainties now present in many hospitals to become less troublesome.

At the present time only one measure of demonstrated merit exists for the management of the infant threatened by hyperbilirubinemia, and this is the use of exchange transfusion. The role of serum albumin in transport of bilirubin and in formation of a prophylactic

complex has suggested that it may have a therapeutic role in conjunction with exchange transfusion. Early observations indicate that when serum albumin is given to the icteric infant, there will be a rise in level of serum bilirubin owing to movement of bilirubin from the extravascular space into the vascular compartment. This rise will, paradoxically, be indicative of protection against kernicterus. The role of albumin in management of hyperbilirubinemia is under active exploration in a number of centers at the present time. It is too early for a categorical statement to be made as to its usefulness.

The indications for exchange transfusion will generally vary with the clinical problem being faced. Its use will often be prophylactic in hemolytic disease of the newborn, rather than dependent upon established high levels of serum bilirubin. Indications for such prophylactic use have been outlined elsewhere,[9] and generally integrate the parameters of maternal history, maternal titer, gestational age, degree of clinical illness at birth, level of cord hemoglobin and/or bilirubin, and/or rate of rise of bilirubin within the first few hours after birth. In infants in whom hyperbilirubinemia does not depend upon hemolytic disease the decision to carry out exchange transfusion will generally be reserved until such a time as the level of serum bilirubin actually approaches an arbitrary dangerous level. The decision will be most difficult when an elevated level of serum bilirubin has no apparently adequate explanation in an infant in whom predisposing factors for hyperbilirubinemia cannot be discerned, where the level of serum bilirubin seems not clearly dangerous nor clearly safe, where confidence in the reports of a given laboratory is not complete, and where, as usual, the likelihood of kernicterus as a complication is impossible to estimate. Under these circumstances we have taken the position that where we are reasonably confident that the level of serum bilirubin exceeds 20 milligrams per 100 ml., a level which is intolerable without respect to its cause, we have carried out exchange transfusions in such infants, at such frequencies and intervals as to keep the level insofar as possible below 20 milligrams per 100 ml. Under this commitment we find that exchange transfusions are done about as often for A or B incompatibility as for Rh, with perhaps half these numbers done for bilirubinemia of some other, perhaps unknown, origin. We generally use donor's blood which is compatible with the mother's serum by the indirect Coombs' technic; such blood will almost surely prove to be satisfactory for management of any unsuspected or obscure blood group incompatibility, as well as for other possible illnesses. We feel that with this policy the risk of kernicterus is minimized for the threatened infant without, until some satisfactory index of the individual's susceptibility to kernicterus becomes available, incurring such risk from exchange transfusion as we cannot afford to take. Needless to say we do not use sulfonamides prophylactically against infections following transfusion, preferring a combination of penicillin and streptomycin, and we regard the entire area of relationship between pharmacotherapy in the laboring mother and her newborn infant deserving of further study as respects metabolism of bilirubin.

Summary

The problem of hyperbilirubinemia in the newborn infant has been reviewed, with attention given to those physiologic handicaps of the newborn infant which normally dispose to an elevation of serum bilirubin in the first few days of life, to those factors which intensify this tendency to hyperbilirubinemia, and to those factors which, in the presence of established hyperbilirubinemia, tend to make the occurrence of kernicterus more likely. It has been emphasized that exchange transfusion offers protection against kernicterus in the newborn infant with hyperbilirubinemia, so long as the level of serum bilirubin can be kept below a threshold level, and the position has been taken that until our knowledge of the pathophysiology of kernicterus is better understood, exchange transfusions ought to be undertaken in the prophylaxis of kernicterus when the level of serum bilirubin exceeds or is apparently destined to exceed 20 milligrams per 100 ml.

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Some Clues in Cardiovascular Diagnosis from Simple Inspection*

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How true! To those of us who had our early experiences in medicine before the days of an expanding number of laboratory and other technical aids, the clues which are there for the asking,—in the history and physical examination—point the path to diagnosis more often than not. This is difficult to teach in the face of physical and chemical methods which may seem to give greater aid because their results have a scientific ring, whether accurate or not, in milliequivalents, micrograms and the like.

IN THE PRESENT AGE of electronics, atomic science, outer space and world turmoil, research is going on at an unprecedented pace. This is particularly true of the physical sciences but applies as well to medical science. The amount of time and money being spent on medical research per year is now 10 times as great as a decade or two ago. New methods and apparatus have been discovered enabling exploration of biologic processes in their most minute details. After a brief period during which these methods are being employed by laboratory investigators only as research tools, they often are taken over by the active clinic and are found to have an important use in the care of the sick. They then quickly become part of the diagnostic and therapeutic armamentaria of our hospitals and medical institutions. The result has been that one procedure after another has been added to the whole fabric of medical care. All this is obviously very expensive. Furthermore, the entire movement of social progress is such that there is no longer much difference between the care rendered to the wealthy and the poor. Expensive medical procedures are becoming more and more available to all.

While the above changes have been going on, changes that have added greatly to the health of mankind, forces of a deleterious nature have insidiously been taking place as well. In the treatment of disease the starting point is diagnosis. This is not only true of medicine but also of all unsolved problems. Cure is difficult without knowing the cause. Sagging of an automobile overpass may not be prevented until is is discovered that some of the pillars and understructures rest on softer ground than was realized. Although diagnosis in medicine is of primary importance, adequate treatment is not always dependent on accurate diagnosis. If the case is one of metastatic carcinoma, it might not matter any, or very much, if the physician had made the diagnosis of arthritis. He still might be giving the patient the same comfort by the use of medication, having made the wrong diagnosis, that he would have attained had he been more astute. Even this is not always true, for a palliative orchiectomy might have afforded considerable relief had it been known that the pains in the bones were due to metastatic prostatic carcinoma rather than chronic arthritis. Furthermore, accurate diagnosis is not vital if the illness is self-limited and not affected by medical care. There are many such diseases that end with complete recovery and for which we have no satisfactory therapy. Diagnosis is mainly of importance when the condition is amenable to cure or help and, if neglected, might be fatal or result in avoidable suffering or disability. At times correct diagnosis is valuable, apart from any therapeutic considerations, when the matter of prognosis is important. This arises in problems of insurance, wills, business ventures, etc.

One might wonder what all this has to do with the main purpose of this discussion. The result of the availability of all these new diagnostic aids is that in the eager search for correct diagnosis, the physician puts the patient, or society, to increasing expense of time and money. What has happened is that simpler

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methods of diagnosis, though possibly less accurate, have lost their vogue and are being neglected. The physician need not worry about the diagnosis in obvious cases. When a patient has marked exophthalmos and a large goiter, the patient himself is likely to know what is wrong. The physician must then concentrate on appropriate therapy. What we are mostly concerned with is the diagnosis that is not quickly apparent. For this we need clues. Only after we have had certain suspicions aroused in our minds do we plan to have tests performed, to rule in or to rule out certain possible diagnoses. When involved laboratory procedures are diagnostic we would like to choose the right one first, rather than first to go through several expensive and troublesome tests that prove useless. These clues are obtained from the customary history of the illness and the initial physical examination that is carried out, together with a few simple laboratory tests, such as a urine analysis and some blood counts. How detailed the questioning and the early laboratory tests will need to be will vary under different circumstances and with different physicians. Of all the pertinent information that is available, that which is obtained by simple inspection is the least expensive and the most neglected. It is this phase of clinical medicine that I now wish to discuss. The observations and references that will be made are based on my own personal experiences. They are obviously limited and will be restricted to some points that happened to interest me. No doubt there are innumerable other aspects of medicine in which valuable but neglected diagnostic clues are available on simple inspection. Most of this discussion will concern features that are related to the cardiovascular system.

In my experience, among all the conditions in which simple inspection has afforded the first clue to a diagnosis long overlooked by competent physicians, masked thyrocardiac disease heads the list. This applies to patients who are seriously ill, with various degrees of congestive heart failure or angina pectoris, and have been treated unsuccessfully by outstanding internists and cardiologists. The diagnosis would be overlooked because there would be no exophthalmos or palpable thyroid gland. In some of these cases a "salmon-colored skin" would be the first clue. It would appear warm, slightly moist, hyperemic and slightly pigmented. A second point might be a unilateral stare to the eyes, and finally, striking gray or white hair which might have started to become gray in the third decade. I need not repeat that simple clues such as these, and others to be taken up later, will not invariably be right. In fact, in most instances they will prove to be useless. However, they can be of great value even if they are only occasionally helpful. They were the starting point in making the correct diagnosis in many difficult cases that came to my attention. In referring to the third of the above points, i.e., early graying of the hair, it must be realized that this also occurs in some patients with pernicious anemia, in others who are prone to early atherosclerosis, and also as a family trait in those who are otherwise well.

Once the suspicion of a possible thyrotoxic factor is aroused in a cardiac by means of one of the above simple clues, the definitive diagnosis can readily be established nowadays by the various laboratory tests that are available. Only then will some patients, previously refractory to treatment and hopelessly invalided, be restored to good health. For this is often an entirely reversible type of heart disease, readily amenable to modern therapy.

The inspection of the tongue was formerly a routine and important part of the physical examination. Nowadays it is much neglected. When patients are ill from almost any cause and the tongue is dirty, coated and furrowed, its appearance will often serve as a useful guide to the progress of the condition. The tongue starts becoming clean and less coated as typhoid fever is waning. The patient who has been ill and confined to bed for a long time with congestive heart failure will often show a clearing of the tongue as the underlying condition improves. Just as we follow the temperature chart, the pulse and respiratory rate, the body weight and the urinary output as guides to the progress of various illnesses, so we can watch the appearance of the tongue in estimating how a patient is getting along.

What is even more important is that the appearance of the tongue has diagnostic value. It has been the first clue to lead me to the correct diagnosis under very critical circumstances. I was once asked by a physician to give him some advise over the telephone, concerning his father, who had been confined to his house with heart failure for several

months. The patient was a farmer, 60 odd years of age, who lived a few hundred miles north of Boston. The son did not want me to make the long trip to see his father, and asked whether any other form of digitalis could help dyspnea when the leaf was ineffective. There was little of value that I was able to suggest, but I realized that a telephone consultation was often quite unsatisfactory and I made plans to see the farmer within a week. The patient had been confined to his farmhouse for several months, spending most of the time in bed or chair. He had been weak and short of breath on effort, had slight edema of the ankles, a regular, slightly rapid pulse, no hypertension or anginal pain, and showed a slight precordial systolic murmur. He did appear a little pale. The first important clue was the appearance of the tongue. Ordinarily a chronic cardiac patient who has been confined to his home for months, who has lost his appetite from taking digitalis and has become constipated from physical inactivity, has a dirty coated tongue. This tongue was perfectly clean, smooth, and a little more red than one would expect with the slight pallor of the skin. It was the kind of tongue seen in pernicious anemia. A few simple blood studies and a gastric analysis confirmed the diagnosis of pernicious anemia. The condition responded splendidly to intramuscular liver injections, the treatment then available, and the patient returned to normal full duty. This was an instance in which moderate congestive failure was the result of anemia and where simple inspection of the tongue quickly gave the clue that led to the correct diagnosis of a curable condition.

The opposite kind of an error can also be made, an error which simple inspection might prevent. I once saw a patient who received treatment with liver extract for 18 months for combined system disease and pernicious anemia. She was a small, thin woman about 60 years old and was under the care of a distinguished hemotologist during this time. The blood findings were not altogether typical and there was partial paralysis of some of the muscles of both arms. The striking feature that struck my attention was that the tongue was deeply furrowed, dirty and coated. It had just the opposite appearance to the type seen in pernicious anemia. In fact, it is very rare to find such a tongue in classical Addisonian anemia. With this thought in mind, doubt was cast on the original diagnosis, and suspicion arose concerning the possibility of a cervical spinal cord tumor. After a lipiodol injection was made into the cisterna magna, x-ray examination showed an obstruction at the upper cervical level. A few days later a neurosurgeon removed a small enucleable dural meningioma and the patient was cured of her paralysis. Here also, simple inspection of the tongue gave the clue that first helped to eliminate one diagnosis and thereby lead to the correct and remediable cause of the illness.

The diagnosis of constrictive pericarditis is often overlooked in general practice. This is true generally because it is not thought of, though at times the diagnosis is difficult and escapes the attention of even the experienced clinician. There are a few features, quickly observed on simple inspection, that may prove helpful diagnostically. If a patient has a fairly normal appearance while sitting or standing, and quickly shows striking suffusion of the face on lying down, one should think of pericardial constriction or tricuspid stenosis. The skin becomes cyanotic, and the veins of the scalp become more prominent and dilated. It would seem under these conditions that the increased venous return resulting from recumbency cannot enter into the right ventricle with sufficient facility. Venous blood, therefore, backs up more readily and distends the venous bed. No doubt, the same features and the same mechanisms are involved in other cases, such as fibrous myocarditis or fibroelastosis, in which the heart muscle expands and contracts poorly.

The second clue to the diagnosis of pericardial constriction is the prominent distended cervical veins one observes in a cardiac patient who is able to lie flat comfortably. This peculiar finding, like the "suffusion sign" just discussed, may also be present in cases of organic tricuspid stenosis. In fact, whenever a patient who is thought to have some form of heart disease has a venous pressure as high as 250 to 300 mm., and yet has comparatively little dyspnea, little if any orthopnea, and shows considerable hepatic enlargement, pericardial constriction is a not unlikely diagnosis and certainly needs to be seriously considered. When both of these above clues are observed on simple inspection, the physician should seek carefully for other evidence, i.e., a defi-

nite third heart sound with a possible visible or palpable apical diastolic rebound, the absence of valvular disease and the possible presence of pericardial calcification on x-ray examination. These two simple clues have served on several occasions to direct my attention to the diagnosis of constrictive pericarditis when it had previously been long overlooked. The outlook in these cases quickly changed from one of gloom to that of hope, as their conditions were greatly helped by surgery.

With reference to the palpable diastolic thrust mentioned above, this feature is similar to the visible bifurcated apex impulse that is often seen in cases that manifest diastolic gallop or left bundle branch block. In fact, there are times when this bifid apex impulse is more easily seen than can the corresponding gallop be heard. This finding can be demonstrated more clearly by holding one end of a straw over the apex impulse and watching the double movement of the other end. By this technic the amplitude of the motion is exaggerated.

There are many well-known simple features readily visible on inspection that are still insufficiently sought for, i.e., the Corrigan hyperactive carotid artery pulsations of aortic insufficiency, the precordial bulge denoting cardiac hypertrophy early in life, the prominent lower jaw and the large hands and spade-like fingers of acromegaly, the pasty, pallid, cow-like placidity of myxedema, the purple skin with clubbed fingers of congenital heart disease, the oval, gray-centered petechiae of bacterial endocarditis and others. They are all helpful hints in cardiac diagnoses.

Some rarer clues that are helpful in diagnosis are less generally known. I recall seeing a boy, 12 years old, who had been treated for congenital heart disease all his life. He has been quite cyanotic since infancy and was therefore protected and inhibited in his activities all these years. He was a little, thin, shy boy with a marked bluish discoloration to the skin. On closer inspection there appeared to be an odd, grayish appearance. On looking at the extended tongue, it was found to be normal in color and there was no clubbing of the fingers. On simple inspection several points were noted to be inconsistent with congenital heart disease of sufficient severity to produce such a high degree of cyanosis. There should have been clubbing of the fingers, and cyanosis of the tongue, and a bluish, rather than a slate-like color of the skin. When the father was asked whether the boy had been given nose drops the entire problem was solved. At the age of a few months the infant had a cold, with rhinitis, and what his physician interpreted as sinus infection. Nose drops of silver nitrate and later, Argyrol, were advised. For some reason this treatment was continued ever since infancy, as a prophylactive measure, so that every night he was given one half a nose dropper full of one or another of these silver containing solutions. He obviously had developed marked argyria. Incidentally, physical examination of the heart, electrocardiograms and radiograph of the chest were entirely normal except for a faint apical, grade one systolic murmur. The harm had been done, for the discoloration of the skin was not reversible, but the outlook for general well-being was excellent. Intelligent, simple inspection might readily have given the proper clues that could have prevented this error early in life.

Another error in the interpretation of cyanosis occurred in a young man of about 20 years of age. He also had been regarded as suffering from some form of congenital heart disease. He complained of fatigue and some breathlessness on effort. The simple clue that aroused suspicion that he did not have congenital heart disease was that with such a high degree of cyanosis, there was absolutely no clubbing of the fingers. He was then observed more carefully in a hospital. Here, all studies of the heart failed to show any abnormalities. However, when some venous blood was withdrawn and oxygen was bubbled through it, the color failed to become arterial. Spectroscopic studies then proved the case to be one of methemoglobinemia. Directly after the intravenous injection of 90 mg. of methylene blue his appearance was normal. The cyanosis disappeared for the first time since birth. He remained well thereafter on the simple administration of about 250 mg. of methylene blue daily in enteric coated tablets and ascorbic acid 1.0 Gm. daily.

There are other, less distinctive features that are detectable on simple inspection which might be mentioned. Some diabetics have peculiar pink, or fairly bright red cheeks on a background of fair skin. Patients with essential hypertension or who are potential hypertensive, very frequently have a bright,

blotchy flush around the clavicles and neck. This flush is commonly observed to develop during the physician's examination. My secretary has often remarked that between the time such patients enter my office and the time they reach the laboratory to have the electrocardiogram and some other tests done, they have become "all flushed up," the color of the neck having changed during my initial history-taking and examination.

Periodic Cheyne-Stokes breathing is often overlooked not only because it is not looked for, but also because deliberate observation for its presence is not made while the patient is asleep. Whenever a cardiac patient is found asleep the physician should not arouse him, but should spend a minute or two watching the breathing. Periods of apnea may be observed that are entirely absent during the waking hours. This observation may be helpful in deciding that certain breathlessness is not bronchial but cardiac in origin, or that insomnia, nocturnal restlessness or breathlessness is due to left ventricular failure.

There is a peculiar type of breathing that I have observed in a very few instances of acute pulmonary embolism, and which I have not noted in other conditions. The patient makes short quick gasps, like a fish breathing out of water. The mouth opens widely but not much air is inspired. This observation might prove helpful on rare occasions. Another peculiarity in breathing that can often easily be detected is the deep sighing, so typical of functional hyperventilation. During ordinary history-taking the patient will be seen to take several deep breaths. Such patients complain of being short of breath at rest and yet take in more air than they need. When this is observed, it is well to stop immediately and ask the patient whether he was breathless that very moment. He will almost invariably answer in the affirmative. This is practically a pathognomonic sign of an anxiety state.

There are numerous other well-known findings that one can observe by simple inspection, some that have a bearing on cardiovascular disease and others that do not. Facial asymmetry, a flattening of one side of the face, a slight droop of one eyelid or one corner of the mouth may direct the attention to an old Bell's palsy, or a previous cerebral vascular lesion. A faint trace of jaundice may be supportive evidence of pulmonary infarction. The long fingers, the high palate and possible changes in the lens of the eyes would quickly bring to mind the diagnosis of Marfan's syndrome with aortic involvement. The transient attacks of cyanosis or flushing of the skin would make one think of carcinoid disease. One might go on at great length enumerating other clues that are within our reach by simple visual observation. It is most important that this aspect of medical diagnosis should be treasured, preserved and even emphasized anew amid the present-day surge of new, complicated and expensive instrumentation that is being introduced into medical practice.

It must be emphasized that certain features observed on simple inspection may only be suggestive but by no means pathognomonic. This is true of the malar flush of mitral stenosis, in contrast to the pallor of aortic disease, the slightly greenish-olive tint of tricuspid stenosis and the stocky, short-necked muscular mesomorphic physique of coronary disease. One may also mention the frequency of freckling in cases of rheumatic heart disease and also as a suggestion of general vascular vulnerability, for undue freckling appears not uncommonly in malignant hypertension. In a word, simple inspection still remains a most valuable tool, though often sadly neglected, in the diagnosis of cardiovascular disease.

Hepatolenticular Degeneration (Wilson's Disease)*

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In less than the fifty years since the recognition of this rare disease as a clinical entity, its metabolic defect has been demonstrated. And as a result of this knowledge a satisfactory therapeutic regimen has evolved with dramatic control of what otherwise becomes a progressively deteriorating syndrome to end in death.

HEPATOLENTICULAR DEGENERATION, since its description in 1912 by Wilson, was considered a veritable archetype of neurologic disease. Certainly, it has an imposing anatomic name as well as an eponymous designation; it is often familial, its manifestations are dramatic and bizarre; its course is one of progressive deterioration, only terminable by death, and until the past decade there was no effective therapy for this disorder. Yet, despite these criteria which would relegate this disease to the museum-piece category, it has been the subject of intense clinical and basic scientific investigation during the past 10 years. Now, within 50 years of its recognition as a disease entity, the means for arresting and reversing its neurologic manifestations are at hand and an approach to the understanding of this disease has been accomplished. In the textbooks hepatolenticular degeneration is now grouped with the metabolic disorders and included among such familiar entities as diabetes and gout. This is an advancement in status from its former obscure position among the "heredo-degenerative disorders of the nervous system of unknown etiology."

In the preface to the first edition of Merritt's *Textbook of Neurology,* Wilson's disease is mentioned as an example of the benefits to be derived from the application of biochemical methods to a study of diseases of the nervous system. From all indications, an approach is being made to the therapy of "inborn errors of metabolism," and even the most therapeutically minded physician will find it necessary to turn his attention toward these previously unassailable diseases.

In 1912, Kinnier Wilson described the association of cirrhosis of the liver and degeneration of the basal ganglia, particularly the putamen, globus pallidus and caudate nucleus. He reported 6 cases, 3 proved by autopsy, and collected 8 others from the literature. He described the disorder as often familial and included among its neurologic manifestations tremor, muscular rigidity, incoordination, dysarthria and emotional disturbances. Although Wilson was not impressed with its significance, the Kayser-Fleischer ring of brownish pigmentation at the periphery of the cornea is now generally recognized as pathognomonic of the disease. This is predominantly a disorder affecting children and young adults. The presenting symptoms may be referable to hepatic disease and, as emphasized by Walshe,[1] this diagnosis should always be considered in otherwise unexplained juvenile cirrhosis. In young adults, tremor is often the initial manifestation, varying from a rhythmic parkinsonian tremor to a movement indistinguishable from that seen in chorea. At times there may be a violent ataxia. When the finger-to-nose test is attempted, the arm, flexed at the elbow, may be alternately abducted and adducted at the shoulder to produce the characteristic wing-beating tremor described by Strümpell as "flügelschlagen." The bizarre character of this dyskinesia and the emotional lability of the patient may lead to an erroneous diagnosis of hysteria or schizophrenia. As the disease progresses the rigidity becomes more pronounced. Mental deterioration, a characteristic open-mouthed smile, drooling, severe dysarthria and muscular contractures eventually become prominent. Neither

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clinical nor laboratory evidence of liver disease may be apparent despite progression of the neurologic disease to the point of invalidism, although the liver disease is thought to antedate the onset of neurologic symptoms. Death may result from progressive neurologic involvement or hepatic insufficiency with coma. Fatal hemorrhage from esophageal varices has been reported.

Pathologic Features

On coronal section of the cerebral hemispheres, the corpus striatum appears shrunken and sometimes presents a brownish to brick-red discoloration. There may be cavitation in the putamen which may occasionally extend into the caudate nucleus. Rarely, the thalamus and red nucleus may be similarly involved. Microscopically there is an increase in cellularity of the putamen due to an astrocytosis. These astrocytes are often large, vesicular cells with one or more basophilic nucleoli. In the putamen and caudate nucleus the nerve cells are reduced in number. In the globus pallidus, in addition to these astrocytes (Alzheimer Type II), there are Opalski cells (large histiocytes) and hemosiderin-laden phagocytes. Focal cortical degeneration is not uncommon in the frontal lobes. Degenerative changes in the dentate nucleus and the brachium conjunctivum have been described.

In sections of the cornea, a row of granules of brown pigment may be seen in Descemet's membrane near the limbus. In a recent histochemical and electron microscope study by Uzman and Jakus[2] these granular deposits were found to be arranged in two parallel zones close to the endothelial surface of the membrane.

The liver may be enlarged early in the disease but is usually smaller than normal terminally. It is coarsely cirrhotic with lobules of varying size. Microscopically a characteristic multilobular cirrhosis is seen, although occasionally the pathologic picture resembles that of subacute hepatitis with postnecrotic scarring.

Biochemical Considerations

One year after Wilson's original description of the disease, in 1913, Rumpel[3] found an increase in the copper content of the liver in a patient dying of this disease. Haurowitz[4] (1930), in a single case, demonstrated conclusively an increased copper content of the liver and brain. Lüthy[5] and Glazebrook[6] confirmed his findings in studies of individual cases.

In 1948, Uzman and Denny-Brown[7] described an amino-aciduria in patients with Wilson's disease. The increase in urinary amino acids in these patients may reach a level of 300 to 800 mg. of amino acid nitrogen per day (or 4 to 6 times the normal). Since there is no associated rise in the amino acids in the blood it is thought that the increased excretion is related to defective absorption in the convoluted tubules of the kidneys. In 1948, Mandelbrote and associates,[8] while investigating the mobilization of copper by 2, 3 dimercaptopropanol (BAL) in multiple sclerosis (regarding the possible connection between swayback and multiple sclerosis), found that one of their controls, a patient with Wilson's disease, exhibited a high urinary output of copper which was greatly increased by the administration of BAL. Glycosuria, uricosuria, phosphaturia and diminished glomerular filtration, in addition to the cupruria and amino-aciduria, have been described in patients with hepatolenticular degeneration.

In 1951, Cumings[9] in London and Denny-Brown and Porter[10] in Boston found BAL to be of value in the treatment of patients with Wilson's disease. Holmberg and Laurell[11] (1948) isolated from human serum a blue protein substance in which copper was combined with alpha globulin. They named this substance ceruloplasmin and found that it could act as an oxidase, employing p-phenylenediamine as a substrate. Ceruloplasmin has a molecular weight of 151,000, each molecule binding 8 atoms of copper. In 1952, Scheinberg and Gitlin[12] found that ceruloplasmin is either absent or present in only very small amounts and has no oxidase activity in patients with hepatolenticular degeneration. It is the deficient ceruloplasmin production in hepatolenticular degeneration which is currently considered to be the primary genetically determined abnormality. Most of the copper in the blood of these patients is loosely complexed to albumin and is readily released by diffusion into tissues with a high affinity for this metal. In the tissues the copper poisons fundamental enzyme systems with resultant cell death in the brain and liver, producing the clinical syndrome. As Walshe[13] indicated in a recent editorial on this subject, the ceruloplasmin theory suffered a major setback when classical instances of Wilson's disease were described with normal levels of cer-

uloplasmin. It has also been demonstrated that there is no correlation between the concentration of ceruloplasmin and the severity of the disease. The alternate theory of the pathogenesis of Wilson's disease has been largely developed by Uzman. He considers the major abnormality to be the formation of an abnormal intracellular protein with an increased affinity for copper. The low ceruloplasmin is attributed to the low plasma concentrations of copper. However, this theory also requires further documentation, although Uzman and his associates[14] reported the isolation of the abnormal protein from the liver of a patient with this disease. Recent isotope work on copper transport has shown that in patients with hepatolenticular degeneration who have a normal concentration of ceruloplasmin, the uptake of radiocopper is abnormal with failure to incorporate the metal into the transport protein.

Treatment

If one concedes that the intracellular deposition of copper is responsible for the manifestations of this disease, the rationale of restricting the amount of copper in the diet is apparent. Foods with a high copper content such as chocolate, nuts, mushrooms, liver and shellfish must be excluded. Copper absorption from the gut can be reduced through the use of an exchange-ion resin or potassium sulfide to promote excretion of copper from the gut. In addition to these measures agents may be administered to effect removal of copper from the tissues. BAL (2, 3-dimercaptopropanol) with two sulfhydryl groups per molecule, by increasing cupruresis, was originally thought to exert its benificent effect through the removal of copper from the tissues. Since the amount of copper removed from the body is now thought by many to be of doubtful therapeutic significance, Walshe[13] suggested that the efficacy of BAL might be related to the sulfhydryl groups which it supplies to the enzyme systems. The amino-aciduria is not affected by this therapy. Since BAL injections are painful and often result in severe urticaria, febrile reactions, nausea and vomiting, and since it is often lacking in effectiveness when employed in the more acute cases of Wilson's disease, a more effective and less toxic type of therapy remained an object of investigation. Engaging in this search, Walshe,[15] in 1956, showed that the sulfhydryl amino-acid, penicillamine (β-β-dimethyl-cysteine) was capable of increasing the urinary excretion of copper in patients with Wilson's disease. Subsequently it was found that urinary copper excretion following administration of penicillamine was greater than that produced by BAL. Since penicillamine is relatively nontoxic and can be given orally, and since prolonged therapy is followed by slow but progressive clinical improvement in many patients, this is now the drug of choice. Attempts have also been made to increase copper excretion with "Versene," high protein diets, cortisone and isonicotinic acid hydrazide (INH), but these agents have not proved to be effective in the treatment of Wilson's disease.

Report of Cases

Case 1. In January 1953, a 21 year old man was admitted to a Naval hospital with a 6 week history of dysarthria and weakness. In April 1953, he was transferred to the Veterans Administration Hospital at Murfreesboro, Tennessee, with the diagnosis "conversion reaction, severe, characterized by mutism." He was first seen in neurologic consultation in July 1953, when no abnormalities other than mutism were apparent. A lumbar puncture and electroencephalogram were not contributory. Subsequently he received a course of electroshock therapy without benefit. When seen for the second time in January 1954, all of the classical manifestations of a basal ganglia disorder were apparent. His face was expressionless with staring eyes. There was a rhythmic, alternating, 4 to 5 per second tremor of the head and hands, as well as athetoid movements of the hands, rigidity at the wrists, anarthria, dysphagia and a tendency toward "wing-beating" when the finger-to-nose test was performed. Saliva drooled from his open mouth, and there was a seborrheic dermatitis over the cheeks and forehead. A faint zone of greenish-brown pigmentation, thought to be a Kayser-Fleischer ring, was seen at the corneal limbus, particularly at the upper pole. His reflexes and sensation were normal. Other aspects of the examination were not contributory.

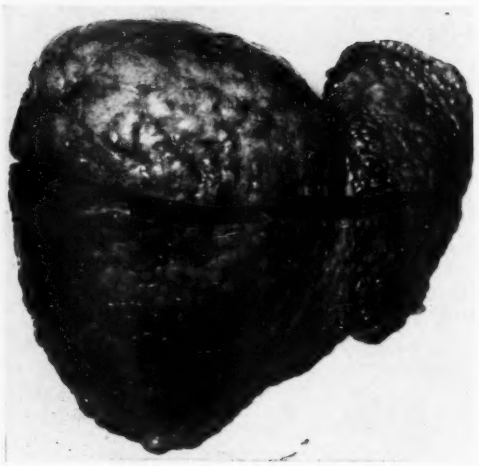
A diagnosis of hepatolenticular degeneration was made, and the patient was transferred to the Veterans Administration Hospital at Nashville for further studies and BAL therapy.

It was subsequently learned that there had been one episode of jaundice 3 years previously. A history of consanguinity in his parents was also obtained, although no family history of hepatic or neurologic disease could be elicited.

Serial electroencephalograms were interpreted as consistent with a generalized cortical dysfunction. The bromsulphalein retention, 45 minutes after a test dose of 5 mg. per kilo., was 11.5 per cent. The cephalin flocculation test was one-plus. All other liver function studies were negative. Slit-lamp examination confirmed the presence of Kayser-Fleischer rings.

Treatment was begun with two 100 mg. intramuscular injections of BAL daily for 10 days each month. Within a few months he was ambulatory and his speech had become quite intelligible. The tremor persisted but was less pronounced. In September 1954, the bromsulphalein retention had risen to 17% despite the

FIG. 1

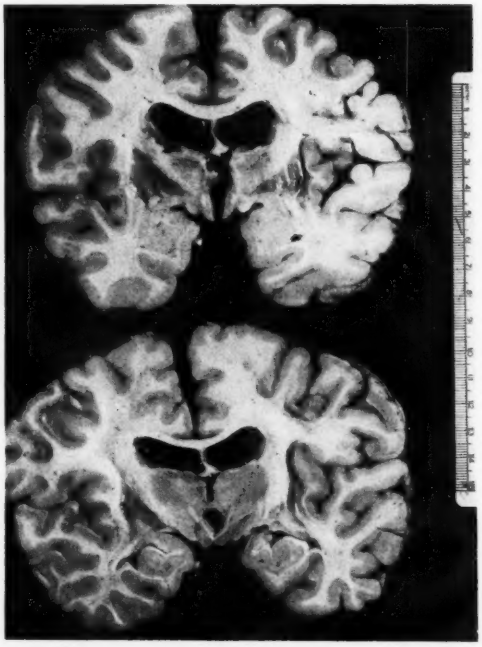


(Case 1) This liver presents a typically cirrhotic appearance. It is shrunken and coarsely nodular.

moderate improvement in his neurologic manifestations.

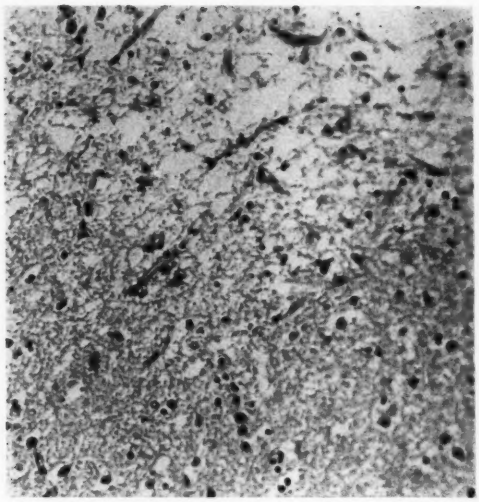
Through a misunderstanding he failed to receive BAL for a period of 4 months and was readmitted to the hospital in February 1955, after becoming much worse. During this interval he exhibited behavioral changes which led to marital discord. After readmission he began to assault other patients and was transferred to the psychiatric ward. He became bedfast and febrile, a gradually deepening stupor ensued, and he expired on May 4, 1955.

FIG. 2



(Case 1) There is symmetrical collapse, fine cystic degeneration and brownish discoloration of the putamen and globus pallidus.

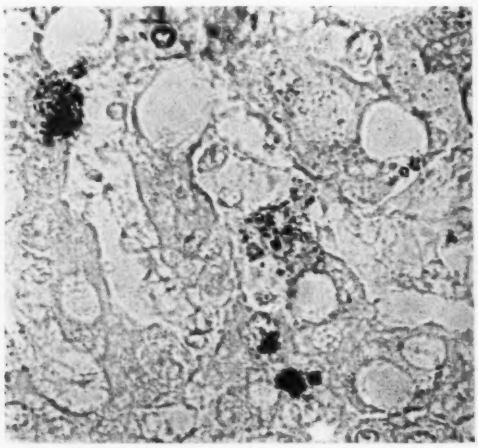
FIG. 3



(Case 1) Microcystic degeneration and gliosis of the putamen (H & E stain).

At autopsy the liver was coarsely nodular, the nodules appearing yellow on section and measuring up to one centimeter in diameter (Fig. 1). The intervening gray fibrous tissue was sparse. The brain weighed 1,520 Gm. and exhibited moderate symmetrical dilatation of the lateral and third ventricles. The lenticular nucleus was bilaterally softened, shrunken and cystic, the puta-

FIG. 4



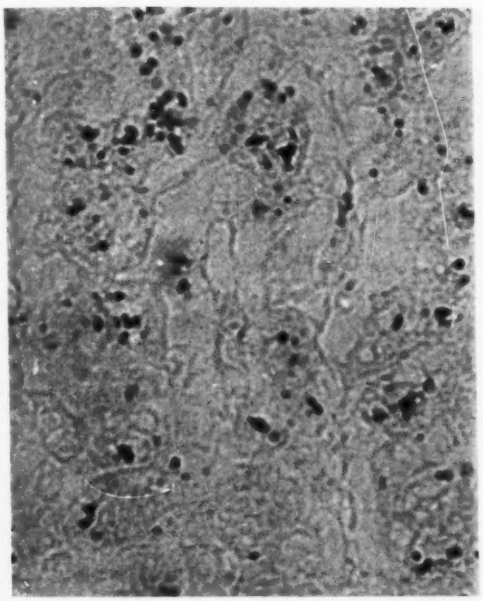
(Case 1) Copper in hepatic parenchymal cells appearing as a black granular precipitate (Rubeanic acid stain).

men being most severely involved on each side (Fig. 2). Microscopically, there was a great increase in astrocytes and oligodendroglia, microcystic change and nerve cell degeneration (Fig. 3). By means of the rubeanic acid stain, as modified by Uzman,[16] it was possible to demonstrate copper in the hepatic parenchymal cells where it appeared as a fine granular black precipitate (Fig. 4). There was also evidence of copper in the putamen (Fig. 5).

Case 2. A 22 year old housewife was seen on Dec. 14, 1954. She presented a 15 month history of tremor beginning in the right hand and had received two series of electroshock treatments without benefit. In the preceding 3 months the tremor extended to involve the left extremities. There was no family history of neurologic disease. Her only sibling was a younger half-brother, her mother having remarried. Her parents were not consanguineous.

Upon examination she was observed to be a tall, slender young woman who exhibited choreiform and athetoid movements of her upper extremities. Her facial expression was not remarkable. When she performed the finger-to-nose test, there was a slight alternating abduction-adduction movement at the shoulder, reminiscent of "wing-beating." Her reflexes, sensation and speech were normal. Fine movements of the hand were not possible. She could not hold a pencil near a pad of paper, and writing was impossible. Although right handed, she was obliged to eat with her less involved left hand. Rapid succession movements were poorly performed with either hand, the effort often exaggerating the dyskinesia in the resting extremities. Cranial nerve examination was not remarkable except for the presence of a dark brown peripheral zone of pigmentation at the limbus of each cornea, appearing most prominent in a crescentic distribution at the upper pole of each cornea (Fig. 6). Her liver was not palpable and the remainder of the examination was not contributory.

FIG. 5



(Case 1) Copper precipitated in area of cystic degeneration in putamen (Rubeanic acid stain).

FIG. 6

(Case 2) Kayser-Fleischer ring. It is characteristically more pronounced at the superior pole of the cornea.

A diagnosis of hepatolenticular degeneration was made, and she was hospitalized on Jan. 10, 1955. Treatment was instituted with intramuscular injections of BAL, 120 mg. twice daily. She experienced considerable pain and tenderness at the injection sites and vomited after almost each treatment, although there was no febrile reaction. She was discharged after a 10 day course of therapy. Within 2 months she began to improve. Her abnormal movements were less pronounced, and she could write a little. Therapy was continued with a 10 day series of daily injections of 120 mg. of BAL on alternate months. She began to gain weight and was able to do her own housework in May 1955. Her menstrual periods became quite regular although there had been amenorrhea for almost one year preceding BAL therapy. However, she continued to eat with her left hand, and the abnormal movements persisted at the left shoulder. In March 1956, BAL therapy was discontinued because her temperature rose to 104°, and she developed angioneurotic edema of the lip following the first injection of the seventh series. Liver function studies continued to be normal, although it was observed at that time that there was an increase in urinary excretion of alpha amino nitrogen.

With the hope that isonicotinic acid hydrazide (INH)

might be an effective chelating agent, this was administered orally in a dosage of 100 mg. 3 times daily in addition to a high protein diet. This therapy was of no benefit, and she became gradually worse. In view of Walshe's[15] early report regarding the effectiveness of penicillamine in promoting the urinary excretion of copper, she was given 500 mg. 3 times daily for 3 days. It was not possible to secure a larger supply of the material at that time, and it was thought then that short courses of this agent might be effective.[17] During the ensuing 2 years she continued to deteriorate and by May 1958, there was a prominent head-nodding tremor. All of the abnormal movements were more pronounced and she was unable to do her housework. She required help in dressing herself and could not comb her hair. Increasing emotional lability added to her difficulties, and these symptoms did not respond to sedatives and "tranquilizing agents." By July 1958, she was much worse than she had been prior to BAL therapy and was becoming despondent. The head tremor was often violent, and she was almost entirely dependent upon her mother for help with many of the routine activities of daily living.

In September 1958, it became possible to obtain D,L-penicillamine in larger quantities. Through the kindness of Dr. Herbert Scheinberg of the Albert Einstein College of Medicine, serum ceruloplasmin levels were determined on two samples of the patient's serum, yielding a value of 10 mg. per 100 ml. of serum. By comparison, the ceruloplasmin level of her half-brother was 39.4 mg. per 100 ml. and her mother's level was 35.8 mg. per 100 ml. The patient's urinary copper excretion rose from 0.165 mg. to 3.315 mg. per 24 hours, a 20-fold increase, 2 days after initiating therapy with penicillamine. On Nov. 17, 1958, she was placed on the following regimen recommended by Scheinberg:[18] (1) a low copper diet, (2) D,L-penicillamine, 1 Gm. daily in four divided doses, approximately two hours before meals and (3) an exchange-ion resin (carbocrylamine resins, Lilly) 15 Gm. at the beginning of each meal. On Feb. 3, 1959, about two and one-half months after this therapy was instituted, she could feed herself again and was able to comb her hair. The head-nodding tremor was barely noticeable, and no wing-beating could be demonstrated. A few weeks later she could drink from a glass with ease and could apply lipstick. Toward the end of May 1959, her handwriting was much improved, and the abnormal movements of the left shoulder were no longer present. She was beginning to sew and crochet and boasted that she could apply fingernail polish without help.

By July 1959, she was able to iron her husband's shirts and was busily engaged in painting porch furniture. Because she was developing some deficiency anemia, the penicillamine and Carbo-Resin were omitted each Sunday, and she received 0.3 Gm. of ferrous sulfate three times daily on that day. Her hemoglobin returned to normal levels and has since remained constantly above 13 grams per 100 ml.

In October 1959, potassium sulfide, 20 mg. with each meal, was substituted for the ion-exchange resin without any adverse effect. The following month she began to work part-time in a "ten cent store." In January 1960, her reputation for steadiness of hand reached legendary proportions, and she was entrusted with the task of taking inventory of the crystal department!

In May 1960, she was working 9 hours a day on weekdays and 11 hours on Saturday in addition to keeping house. On July 27, 1960, she was able to do some intricate sewing while a motion picture camera recorded the achievement. Only upon rapid alternating movements of her extremities could any neurologic dysfunction be detected by September 1960. The Kayser-Fleischer rings persisted but were less pronounced. Her general health was excellent, and she continued to work long hours as a saleswoman and housewife.

Discussion

The rapid deterioration of the young veteran in Case 1 is characteristic of the acute type of hepatolenticular degeneration. The BAL therapy did not result in as striking an improvement as that noted in Case 2 and he expired within two and one-half years following his initial symptoms. The postmortem findings were also characteristic of the acute type of hepatolenticular degeneration with cystic changes in the putamen. Neither the gross nor the microscopic changes were different in any detail from those reported in untreated cases. In Case 1 the abnormal bromsulphalein retention and a history of transient jaundice a few years previously contrast sharply with the absence of any laboratory or clinical indication of hepatic dysfunction in the second patient. Her history is more consistent with the chronic form of the disease, and her response to treatment was much more dramatic. Penicillamine proved to be most effective therapeutically in all respects. There were virtually no side-effects save for a transient iron deficiency anemia which was easily corrected.

Since penicillamine is known to be a pyridoxine antagonist and since three cases of granulocytopenia were described in patients receiving penicillamine, Walshe[19] questioned whether pyridoxine should not be added to the regimen. It is of interest that three electroencephalograms, two before treatment with penicillamine and a third taken 6 months after treatment was begun, were entirely normal. She has not experienced any alteration of consciousness during the 2 year period of penicillamine treatment in contrast to patients with known pyridoxine deficiency who may exhibit electroencephalographic abnormalities and convulsions.

As Cartwright and his associates[20] have recently indicated, the diminished ceruloplasmin does not seem to be the essential determining factor in hepatolenticular degeneration. They emphasize the fact that in 6 of 28 patients with

Wilson's disease the ceruloplasmin levels were as high as the values in two normal controls. They pointed to the poor correlation between the ceruloplasmin level and the severity of the clinical manifestations. Improvement after treatment of the disease is not associated with an increase in the ceruloplasmin level. A diminished ceruloplasmin is also encountered regularly in the newborn, in patients with nephrosis and in infants with an idiopathic hypocupremia. A rise in ceruloplasmin following estrogen treatment in one patient with Wilson's disease and after pregnancy in another was not associated with clinical improvement. They concluded that "a deficiency of ceruloplasmin is not the single uncomplicated determinant of the disease" and that the Kayser-Fleischer corneal ring is the most reliable diagnostic feature of Wilson's disease.

In spite of the extensive and varied approaches to the problem of hepatolenticular degeneration, some of the basic questions regarding its pathogenesis remain unanswered. Yet, an encouraging advance has been made toward the therapy of a disorder for which no treatment previously existed.

Summary

1. The clinical and pathologic features of hepatolenticular degeneration are described, and the biochemical investigations relating to this disorder are reviewed.

2. The various therapeutic approaches and their rationale are discussed.

3. Two cases representing the acute and chronic types of this disorder are presented. One case came to autopsy and copper was demonstrated histochemically in the basal ganglia and liver. The other patient received BAL for several months with moderate improvement. It was necessary to discontinue BAL because of a hypersensitivity reaction, and she has now been treated with D,L-penicillamine for more than 2 years with almost a complete remission of symptoms.

Acknowledgment

I am indebted to Dr. I. H. Scheinberg of the Albert Einstein College of Medicine in whose laboratory the urinary copper excretion and the ceruloplasmin levels were determined. The therapeutic regimen employed in Case 2 was suggested by Dr. Scheinberg.

D,L-penicillamine was obtained from the Aldrich Chemical Company, Milwaukee, Wisconsin, through the courtesy of Dr. Alfred Bader.

The supply of Carbo-Resin was contributed by Eli Lilly & Company, Indianapolis, Indiana.

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Acquired Strabismus in Adults*

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The author urges a more active and definitive approach on ophthalmologists in the management of acquired strabismus in adults. Apparently, since they had fused vision before an ocular defect, they may again develop such if the surgeon will help them on the way by operative procedures on the extraocular muscles.

OCULAR DEVIATIONS which develop in adults are in marked contrast to those generally seen with childhood strabismus. Most children with strabismus have static horizontal heterotropias which are comitant and without significant vertical elements. There is often total lack of fusion and no diplopia, and there may be accompanying amblyopia. Except for the accommodative component the etiology is unknown.

Adults with acquired strabismus present complaints consisting of diplopia and inability to suppress. There is usually incomitance with often a significant vertical element. When the deviation is neutralized fusion is present. In the majority of cases the patient can date his ocular defect to an underlying disease or incident, such as trauma. As the patient's course is followed, there frequently is a change in the amount and direction of his deviation.

Since these patients have had binocularity up until the time of the development of strabismus, it would seem that the opportunity for obtaining single vision would be good, and that if their visual axes were aligned by a surgical procedure, the patient would be relieved of the bothersome diplopia. In our experience this has been true, and these cases present an excellent opportunity for a functional result.

It is not possible to obtain good results in all patients due either to the severity of the deformity or progression of the disease. For this reason certain factors must be evaluated before definitive therapy can be attempted. These are: (1) remaining functional reserve, (2) status of the underlying etiology, and (3) magnitude of the ocular deviation.

To improve motility there must be sufficient function remaining in the extraocular muscles. For example, a sixth nerve palsy affects only the lateral rectus, whereas a third nerve palsy involves 4 extraocular muscles plus the levator. The prognosis for a functional result is excellent in the abducens palsy and poor in the complete oculomotor paralysis.

Before undertaking treatment it is necessary to determine the exact cause of the heterotropia. The evaluation of these patients often involves the services of the neurologist, neurosurgeon, and internist, as well as the ophthalmologist. In addition, diagnostic adjuncts such as radioactive iodine uptake, Tensilon testing, skull and orbital x-ray studies, and blood chemical determinations should be obtained. In many instances electromyography of the ocular muscles is helpful. It is also necessary to establish that the process is at a standstill and will remain so. This latter point is of particular significance in cases of nerve palsy, dystrophy of the extraocular muscles, and thyroid myopathy.

In extremely large deviations it is often impossible to obtain single binocular vision, even with extensive operations and using the maximum amount of prismatic correction. In general, patients with over 50 diopters of deviation in any direction fall within this group.

The cases to be reported have been subdivided into: (1) nerve palsies, (2) adhesive syndromes, (3) thyroid myopathy, (4) progressive dystrophy of the ocular muscles, and (5) myasthenia gravis.

Trauma

Nerve Palsies—

(1) *Sixth Nerve Palsy.* In patients in whom there is a sudden onset of inability to abduct an eye past the midline, one assumes that a paralysis has developed in the lateral rectus. Gradually re-innervation may be seen with

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FIG. 1

(A) Before operation. (B) After 5 mm. recession of right medial rectus.

complete return of function. In instances where there is absent or incomplete return, the assumption is made that a partial or complete paralysis still exists.

Evaluation for a period of one year is usually required before the possibility of re-innervation seems unlikely. Electromyography performed at this time is quite revealing in that some patients appear to have had complete return of activity in the lateral rectus, and the eye is held in the esotropic position by a contracted medial rectus.

Therefore, it is possible to divide lateral rectus paralysis into 2 groups, one of which has a pseudoparalysis and esotropia due to the contracted medial rectus; the other group has a remaining paralysis due to abducens nerve or lateral rectus involvement. The following cases illustrate this point and demonstrate the advantage of determining this prior to operation.

The *first type*, with a functioning lateral rectus, is illustrated in the case of a 24 year old woman who was thrown from a horse at the age of 17 (Fig. 1,A). No skull fracture or neurologic deficit was demonstrated except for a right sixth nerve paralysis which had not changed clinically. Electromyography demonstrated a normal pattern for the lateral rectus with good recruitment on attempted abduction (Fig. 2). At the time of operation the medial rectus was contracted, as evidenced by attempted forced ductions, and the right medial rectus only was recessed. The postoperative result is shown in figure 1,B.

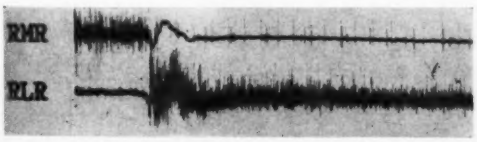
The *second type* of patient is seen in figure 3,A. This was a 45 year old woman who was in an automobile accident in December 1957, which produced a right skull fracture involving the right orbit and right mandible. The residual damage consisted of a complete right sixth nerve palsy, right fifth nerve anesthesia, aberrant regeneration of the right seventh nerve, and a minimal right hemiplegia. Electromyography done in November 1958 showed an almost complete paresis with only a few scattered motor units (Fig. 3,B).

At operation, Nov. 8, 1958, the right medial rectus was found to be contracted by forced duction test. This muscle was recessed 5 mm. The right superior rectus and right inferior rectus were transplanted in their entirety 8 mm. temporally. Following the operation the patient developed atrophy of the lateral one half of the iris. Thirty degrees of abduction was obtained with single binocular vision straight ahead (Fig. 4).

The recession of the medial rectus was elected for 2 reasons: almost complete absence of activity in the lateral rectus by electromyography, and contracture of the medial rectus demonstrated by forced ductions.

2. *Partial Third Nerve Paralysis.* Patients with partial third nerve paralysis may be managed similarly. In the event a contracted mus-

FIG. 2

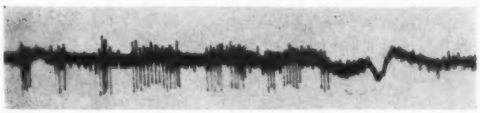


Electromyography of right medial and lateral recti showing normal pattern of innervation.

FIG. 3, A

Case of a lateral rectus palsy before operation.

FIG. 3, B



Electromyographic tracing obtained from patient in figure 3,A. Lateral rectus contains only a few scattered motor units indicating almost total paralysis.

FIG. 4

Result following Hummelsheim type of operation.

cle is found, and there is electromyographic evidence of function in its antagonist, the contracted muscle may be recessed. In the face of paresis it is necessary to resect the paretic muscle and recess its antagonist, unless a Hummelsheim type of operation is planned.

Adhesive Syndromes—

Quite frequently following trauma, an orbital hemorrhage will be noted which can even produce proptosis. With absorption, adhesions may form between the ocular muscles and the globe or the orbit. It may be possible to localize the adhesion to one area of the orbit.

An example of this is a 46 year old woman who was in an automobile accident that produced marked ecchymosis about both eyes, but more so on the right. One month following the accident the patient was aware of vertical diplopia which increased for 6 months. This was much greater when she looked up than when she looked down. A corneal leukoma ascribed to measles had been present from the age of four.

The findings resemble those of a superior oblique sheath syndrome (Brown Sheath syndrome) with the patient unable to elevate the right eye in adduction (Fig. 5,A). By electromyography there was no loss of activity in the right inferior oblique (Fig. 5,B). In primary position there was 10° of left hypertropia that increased to 25° in upward gaze. An exotropia of 20 diopters was also present in primary position, and this increased to 40 diopters looking down.

At the time of operation it was impossible to elevate the right eye in adduction in the up and in position.

FIG. 5, A

Adhesive syndrome of the right superior oblique.

FIG. 5, B

Increasing activity of the right inferior oblique without further elevation of the globe.

Some elevation was obtained in the up and out field. An attempt was made to withdraw the tendon sheath of the superior oblique, but it was found adherent to the roof of the orbit. This was dissected free and a tenotomy performed just nasal to the superior rectus. The right inferior rectus was also recessed 4 mm. The postoperative result is shown in figure 6. It was necessary to use 8 diopters of vertical prism to correct the patient in primary and down gaze for distance; no correction was required for near. She was fitted with vertical prisms in her driving glasses and has maintained binocular vision.

In patients with adhesive syndromes it is almost impossible to decide upon the surgical approach from the ocular examination. The previously mentioned patient would appear to have had an inferior oblique paralysis, whereas actually she had superior oblique adhesions. Forced ductions are a necessity to differentiate adhesion or contracture from paralysis. It is only by electromyography that the possibility of complete paralysis can be eliminated, since it may exist concomitantly with contracture or adhesion. At the time of the surgical procedure exploration must be done in all areas where there is suspected contracture, fibrosis, or adherence. These findings in turn can be used for a more definitive approach to the operation.

FIG. 6

After tenotomy of the right superior oblique and 4 mm. resection of the right inferior rectus.

It must also be remembered that fractures involving the floor of the orbit may produce bizarre vertical deviations. The injury may be accompanied by adhesions to the inferior orbital muscles as is seen in a "blow-out" fracture. A fracture of the inferior portion of the orbit may also produce a downward displacement of the globe which results in a hypotropia. This type of injury requires reconstruction of the floor of the orbit by a cartilage or bone graft. Often vertical muscle surgery must be done secondarily.

Thyroid Disease

It has been well documented that changes occur in the ocular muscles with alterations in thyroid function. The underlying lesion appears to be an ocular myopathy with the presence of chronic inflammatory cells, degenerative changes in the muscle fibers, a deposition of abnormal ground substance between the fibers, and denervation atrophy. Alterations in ocular motility may be produced by several mechanisms, the most obvious being a paralysis due to pressure upon a nerve. The deposition of ground substance may also produce limitation in the muscles. Another possibility is adhesions developing between ocular muscles due to chronic inflammation. The 2 sites available

FIG. 7

Inability to elevate globe above midline due to thyroid myopathy.

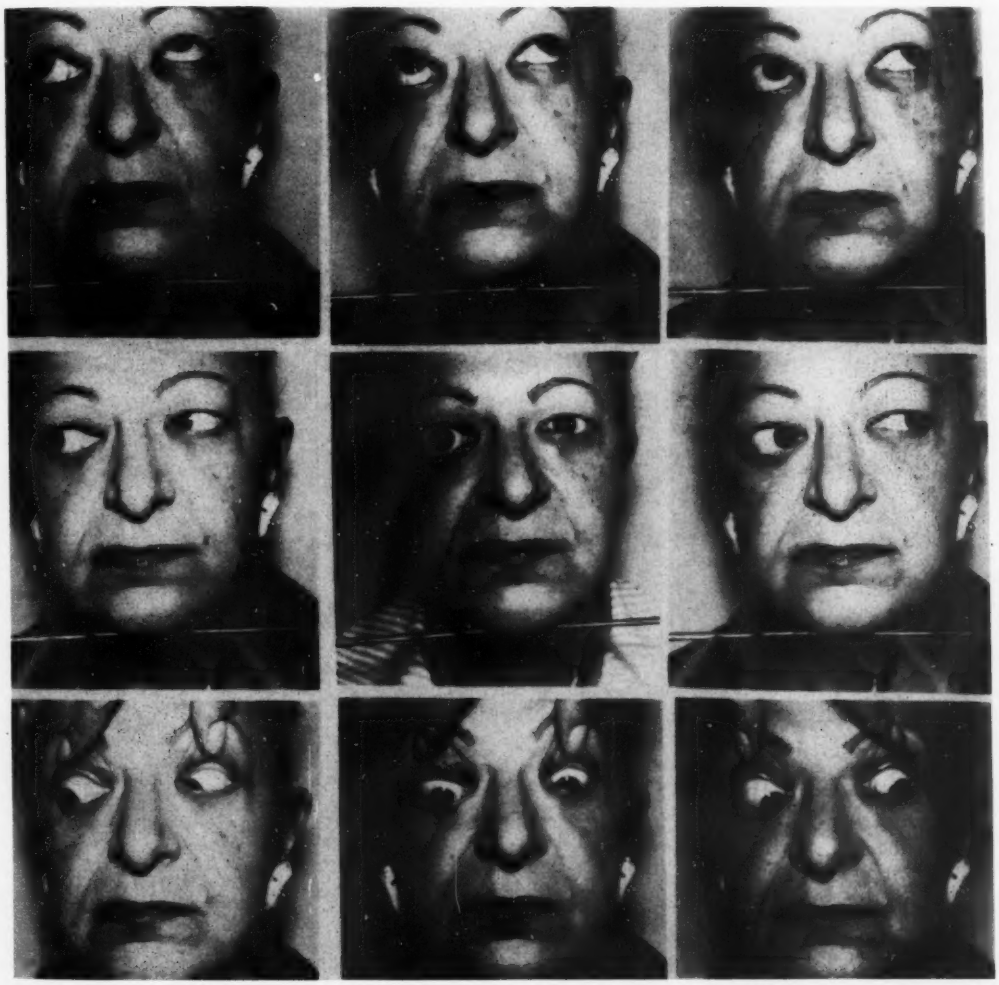
for this are the contact between the inferior oblique and the inferior rectus, and the superior rectus and the levator. This produces 2 problems seen in thyroid myopathy; namely, inability to look up due to the adherence of the inferior oblique and inferior rectus, and superior lid retraction on upward gaze from involvement of the superior rectus and the levator.

From a motility standpoint only the former need be considered. This type of patient presents with a picture that resembles more a superior rectus palsy than an inferior oblique palsy. There is greater limitation in up and out rather than up and in gaze. Generally there is adequate activity in the superior rectus or inferior oblique by electromyography. Attempts to rotate the globe upward are quite revealing in that resistance to upward movement is found, particularly in the field of action of the superior rectus.

A patient who presented the above problem in a unilateral fashion is described as follows.

A 51 year old woman was diagnosed in May 1957 as having "thyrotropic exophthalmus" (Fig. 7). This was accompanied by congestion in both eyes, but more marked on the right. She was hospitalized for an endocrinologic evaluation, and the presence of hypothyroidism was established. Therapy consisted of dessicated

FIG. 8



Results following recession of the right inferior and lateral recti. Adhesions to the inferior orbital margin were also severed.

thyroid and a trial of cortisone. There was no change in the proptosis since January 1958, when a 4 mm. difference had been observed. At the time of our evaluation she demonstrated 35° of right hypotropia in primary position. This increased to 50° on upward movement. There was more limitation in the right eye in the up and out rather than up and in position. An overshoot was observed in the field of action of the right inferior rectus and right superior oblique. Eight degrees of right exotropia was also noted on gaze right.

At the time of operation she was found to have dense adhesions between the inferior rectus and inferior oblique. Bands were also noted extending from the inferior oblique to the orbital margin. All of these were sectioned. The inferior rectus was recessed 5 mm. and the lateral rectus 7 mm. Six months following operation the patient's eyes were straight in primary position with 3° of right hypotropia on upward gaze, and one on downward gaze. Two to three degrees of right exotropia were noted on extreme gaze to the left (Fig. 8). No prisms were required.

Clinically these patients appear to have involvement of the superior rectus, whereas actually the globe is adherent below. Once this is recognized, a very complex problem can be managed by a single muscle procedure; namely, recession of the inferior rectus with lysis of adhesions to the inferior oblique. It is also wise to check for similar adherence to the inferior orbital margin since failure to relieve this may produce retraction of the lower lid after recession of the inferior rectus.

In the event that no limitation of upward motion is found by forced ductions, then more definitive muscle surgery should be used,—namely, resection of the underacting muscle. With severe involvement a recession of its antagonist must be done in addition.

Progressive Dystrophy of the Ocular Muscles

This is an unusual involvement of the ocular muscles by a dystrophic change with a gradual loss of individual muscle fibers. Quite often it occurs in families with the onset in early adulthood. The patients generally present with the complaint of ptosis. Diplopia is rarely seen due to the symmetrical involvement of all of the ocular muscles. There is almost complete immobility of the eyes, with the eyes being fixed straight ahead. The facial muscles are commonly involved, producing a "mask-like" appearance. In addition, there may be atrophy in the shoulder girdle musculature. Satisfactory results may be obtained from ptosis surgery.

The clinical picture before and after ptosis surgery is illustrated in figure 9 of a 46 year old woman with a history of loss of ocular movement dating to her late twenties. She also

FIG. 9

(A) Example of progressive dystrophy of the ocular muscles. (B) Following 8 mm. resections of the levators.

had a sister with a similar problem. An 8 mm. levator resection was done in each eye with a satisfactory cosmetic and functional result.

There may be asymmetrical involvement producing a heterotropia. This is seen in the case of a 43 year old man with a 22 year history of uncrossed diplopia upon looking to the left (Fig. 10,A). This had progressively increased up to the present. In addition, a ptosis was noted on the left side. There was also loss of downward gaze as well as a lack of convergence. The results following a left levator resection and a left lateral rectus resection are shown in figure 10,B.

It is well to remember that resections of smaller magnitude give larger response in these patients since the antagonists are involved. In the above instance the lateral rectus was resected 5 mm. for 20 diopters of esotropia. Also the levator resections must not be the maximum 12 to 14 mm., but about half this amount.

Myasthenia Gravis

The above condition may resemble several diseases involving the ocular muscles. Often there may be progressive weakness of a single ocular muscle in one or both eyes without generalized symptoms. The disease tends to be progressive with later involvement of other ocular

FIG. 10

(A) Asymmetrical involvement of progressive dystrophy of the ocular muscles with unilateral ptosis and limitation of abduction. (B) Two months following 7 mm. left levator and 5 mm. left lateral rectus resection.

muscles, and for this reason intracranial neoplasms are often considered. The diagnosis is not difficult in patients with myasthenia involving the skeletal muscles. However, the diagnosis is frequently missed where ocular symptoms predominate. The administration of 10 mg. of edrophonium chloride (Tensilon) is usually diagnostic since there will be an almost total return of ocular motility within 30 seconds. This drug seems to have a particular affinity for the ocular muscles and has less side effects than prostigmin. Often electromyography and cholinergic testing are combined.

The results before and after edrophonium chloride are illustrated in figure 11.

This 45 year old man had both horizontal and vertical diplopia for 2 years. In addition, a left ptosis had been present for one year. There was lack of elevation on gaze to the right, particularly in the left eye. Following Tensilon there was complete return to normalcy. This patient had had a neurosurgical evaluation for the possibility of a brain stem lesion. The diagnostic tests included arteriograms. His ocular motility was normal following Mestinon therapy.

It is well to consider myasthenia in patients who present a multiplicity of ocular muscle involvement. This is particularly true if there is an increase in symptoms occurring late in the day. Often the ocular complaint may be the only evidence of the disease.

Conclusion

Before any definitive surgery is attempted in acquired strabismus in adults, a diagnosis of the underlying process must be made. The investigation of the patient is often one that involves many specialties. In the majority of cases the underlying disease can be determined and this, in turn, will affect the surgical procedure and prognosis.

Again it is emphasized that the disease process must be at a standstill, with very little opportunity for further progression. Otherwise additional operations may be required for an increasing or decreasing deviation.

In patients with an adhesive syndrome in the orbit, it is often impossible to decide preoperatively on the type of operation necessary. These individuals must be evaluated upon the operating table by forced ductions and exploration of any suspicious limitation. This evaluation must be as atraumatic as possible since postoperative adhesions will be as bothersome as those found preoperatively.

The results following operation in adults with acquired strabismus have been excellent in that the patients usually obtain single binocular vision in the primary and depressed position. Often there is some remaining deviation in upward gaze, but this is satisfactory since elevation is a rarely used position. Observation in this report has also been made that a small remaining strabismus will decrease with the passage of time and the patient become binocular. Presumably, if almost complete alignment is obtained, the patient can accomplish the remainder. Small prismatic corrections are useful in the recovery interval.

FIG. 11

(A) Patient with myasthenia gravis attempting to look up. (B) Following Tensilon administration.

Discussion (Abstract)

Dr. Lawrence T. Post, Jr., St. Louis, Mo. Dr. Miller's most significant contribution in my opinion is his conviction that acquired strabismus in adults is amenable to treatment, and that surgical management should always be contemplated if there is not too obvious a risk of making matters worse.

Whiter and wiser heads may look on all of this as simply a case of "fools rushing in where angels fear to tread," but we have seen such dramatic improvement in cases considered by other physicians to be untreatable that we now make every effort possible to improve patients with acquired strabismus. The reason for the usual reticence is not difficult to discern. Many of these cases are complicated, the picture is frequently confusing, and most involve some vertical muscle imbalance; the last is reason enough for shyness as far as most ophthalmic surgeons are concerned. However, as is pointed out in the present paper, the vitally important consideration is that these patients have previously had the ability to fuse, and they can acquire it again much more readily than, for example, the child who has never fused before. Results of operation for vertical disturbances in these patients are frequently beyond the surgeon's fondest expectations. Much of this can be attributed to a remarkable ability of the neuromuscular apparatus to readjust itself, once the greater part of the physical obstacle is removed. About 2 years ago I operated on a woman who had been in an automobile accident, suffering orbital hemorrhages and perhaps direct contusion injuries to the eye muscles. The vertical muscle imbalance was irregular and seemed to fit no diagnostic pattern. It was virtually impossible to be sure whether we were dealing with muscle weak-

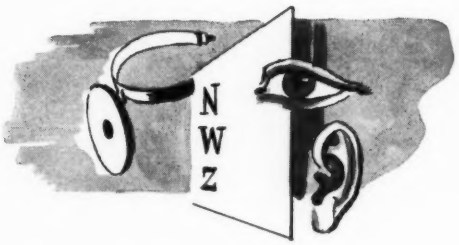
nesses, fibrosis or even spotty neurologic defects. She could fuse only looking far up and to the right, and consequently she wore a patch over the right lens of her glasses, which had a little window in the upright position. It was assumed that a 2 or 3 stage procedure would probably be necessary. One other physician had strongly advised against operation. An oblique recession-resection-type of procedure was carried out. Surprisingly, the patient was almost immediately able to fuse in the primary position, but there was such a marked incomitancy that she continued to have diplopia in most fields of gaze, especially with the eyes depressed. From visit to visit, however, the fusion range increased astonishingly, and the eyes became more nearly comitant. Now, almost one year after the fact, she is almost perfectly comitant, and she fuses in all but the very extremes of gaze.

This patient simply illustrates the fact that, even with quite bizarre imbalances, if the eyes can be brought reasonably nearly in line, the ability of solid fusion, which these patients have had previously, seems to come to the surgeon's assistance and permit his admittedly crude surgical procedure to result in a correction difficult to explain on a theoretical basis.

I would take very minor issue with the suggestion that a progressive condition must be allowed to reach a standstill before surgical treatment is contemplated. There are certain myopathies, for example, involving slow changes for the worse, sometimes over a matter of years; an indefinite delay in treatment might then result. I have a patient with a progressive vertical imbalance, which over a period of 20 years gradually increased from a hyperphoria of 10 prism diopters to about 30; with this was a progressively more marked and distressing head tilt to maintain fusion. No diagnosis was ever made, despite 2 hospitalizations for study. Finally, operation for oblique imbalance was performed. Again the initial correction was not as good as the eventual. She has no head-tilt now, and only a very slight vertical phoria, which she overcomes without symptoms.

In most communities, where electromyography is not available, other tricks must be relied upon to help differentiate between a muscle palsy and a contracture or fibrosis of a muscle. It might just be mentioned that, in addition to the forced duction test mentioned by Dr. Miller, a Duane's type of lid fissure alteration is sometimes a valuable presurgical clue.

I hope that Dr. Miller's remarks will make eye surgeons a little less timid for, both cosmetically and functionally, there is practically nothing to lose and very much to gain. I believe the horror of a near-miss and permanently distressing diplopia is considerably exaggerated.



Communication and Understanding*

J. MAXEY DELL, JR., M.D., *Gainesville, Fla.*

MEDICINE HAS ADVANCED SO MUCH on the scientific side and so much information is available that it seemed I might contribute something on the subject of communication and understanding between physicians, which might be of more value than anything I might offer from a scientific study. The reason for this presentation is the misunderstanding and misinformation so apparent in talking every day with other doctors.

Mrs. Jones was injured and her ribs were studied by a radiologist, in a city of 30,000, with negative findings. Mrs. Jones returned to her home town and a week later her family physician sent her to another radiologist, who found a fractured rib and reported it. The patient asked her family physician why the first radiologist did not find the fracture, and perhaps he honestly answered, "I don't know."

Mrs. X. goes to a radiologist for an upper gastrointestinal series which is reported negative. She continues to have symptoms, a surgeon feels a mass and at laparotomy finds retroperitoneal Hodgkin's disease or lymphosarcoma. Unless the surgeon is very careful in explanation, the patient and her friends will believe she has cancer of the stomach. Subsequent talk may well revolve around the radiologist not finding a "stomach cancer" though there is a cancer which will kill her shortly. This type of case is encountered in all fields of medicine, and if misconceptions or erroneous ideas are permitted to remain and conditions in need of explanation ignored, another criticism of medicine has occurred at a time when we need less of this.

A patient sees Dr. X. who on auscultation finds nothing in her chest. Twelve hours later Dr. Y. finds obvious consolidation. Should he explain why Dr. X. did not find it or should he become a hero and expert diagnostician by his silence? This is also true of many x-ray studies and often one should be thankful he was not the first physician to study the patient.

Often the matter of patients returning long distances for check-up or periodic follow-up examinations in the large clinic might be looked into; more communication with the local physicians might result in lessened visits. Complete and thorough studies by the local physician or tumor clinic, with a full and complete report to the large clinic are, of course, essential. It is also essential that the large clinic be specific in what it desires by way of a follow-up, which certainly may save many and expensive visits.

I urge every radiologist to make a determined effort to acquaint his fellow practitioners with his limitations, potentialities and his problems. I beg radiologists, as a group, to explain through talks and through papers the many facets of radiology.

For the clinician to gain full benefit from the Roentgenologic Service he must know its possibilities and its limitations. He should know what is done on routine examinations, what is omitted, what the roentgenologist does and what he considers an adequate examination. We must also understand what each other is talking about. It is important that the roentgenologist, the clinician and the technician use the same language, at least locally. This is illustrated most strikingly by the specialist who orders work in some other field. The entire field of medicine touches, at some time, each individual specialist. The limitations of roentgenology should be known by every physician since we often neglect to extend the report, "No abnormality noted in the intravenous urogram, but this does not rule out tumor, carbuncle, etc.," or "Examination of the tibia shows no abnormality, but this does not rule out an early osteomyelitis."

To be concrete, let us start with roentgenography of the urinary tract. There are two main methods of investigation,—the intravenous urogram and the retrograde pyelogram. These are complementary and not supplementary examinations. The intravenous urogram is of prime importance in studying the excretion and transportation of the dye. It shows the normal status without the introduction

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of reflex manifestations, such as spasm of the ureter. It is extremely valuable in the diagnosis of the small stone in the lower ureter, in evaluating strictures and dilations of the urinary tract. The degree of dilation of the urinary tract in retrograde studies is to some extent dependent on the pressure exerted in injecting the media. In the diagnosis of tumors, tuberculosis, carbuncles, pyelonephritis, polycystic disease, single cysts or any condition in which the anatomic contour must be complete, the retrograde pyelogram is at times superior. The referring physician should know the importance of allergic reactions in relation to I.V. urograms, the futility of doing an I.V. urogram in patients with nitrogen retention above a certain level and that preparation of the bowel is still needed in retrograde studies.

We need to find out what the doctor means when he orders a "barium swallow," but what we wish that doctor to know most of all is that we occasionally miss small or tumors of moderate size in the fundus, ulcers on the posterior wall and in the pyloric canal, and that we cannot diagnose esophagitis with any degree of regularity. We must make it understood that we need to re-examine patients just as the cardiologist or the general practitioner needs to listen to the heart the second time. The referring physician must understand that the stage of development of the disease determines at times the level when radiologic diagnosis becomes evident on the film, just as does the consolidation of pneumonia, the rash of measles or the inversion of the T-wave. A gastric or duodenal ulcer after 7 days to 10 days of treatment may be healed to the point where it is no longer detectable, and yet too often we examine patients after treatment for even longer periods. It is well to know that in some cases of gastrointestinal bleeding with anemia in which the patient is negative radiologically, the physician may diagnose duodenal ulcer with a high degree of accuracy if a high gastric acidity is present. What does the clinician mean when he orders a G.I. series? Does he think you will do a barium enema as well as an upper G.I. series? If you know there has been bleeding in this case and that the stools have been tarry but have not contained bright blood, should an enema be done? Does bright blood in the stool ever come from the stomach? Most of you know that bright red blood from the stomach may appear in the stool with rapid transportation in the intestinal tract. Should we do a small bowel series in the case of the patient who is bleeding, but in whom the upper G.I. series and colon are negative? Should we merely send a report to the physician or should we call him and discuss the case with him? The latter is done too infrequently. Does the referring physician know the indications for a small bowel study and how detailed and time consuming it is? We all realize the radiologist will not be present at every examination and that the technician will, at times, do the work in his absence. The technician will depend on the referring physician for information. We need to train our technicians what to ask for. As an example,—"the doctor orders a flat-plate of the abdomen." We may beg the physician to give us the condition to be ruled out, but still we often do not receive that information as a routine. The most tactful and most acceptable question for the technician is, "Doctor, do you want me also to take an upright film for bowel obstruction, or a higher upright for air under the diaphragm or would you like both?" If the doctor says, "Yes, but I do not think the patient can stand," then the technician may tell the doctor the same purpose can be accomplished by a decubitus film. Perhaps the doctor may say, "No, I am looking for a gallstone or a kidney stone." Then we may take the appropriate film.

At times, we miss a small gallstone, a small polyp of the colon and often bleeding lesions of the small bowel. This information is needed by the physician so he may order a second examination. I believe it would be correct to say the diagnosis of gastritis belongs to the gastroscopist, proctitis to the proctoscopist and the very early diagnosis of colitis to the clinician. It is probably a waste of time to do a cholecystogram or a cholangiogram in the presence of a serum bilirubin of over 5 mg. per 100 ml. Certainly all roentgen studies of the gallbladder and biliary ducts with contrast media are useless in the presence of frank jaundice.

Most radiologists have a routine for skull injuries that consists of a PA., AP., right and left lateral and perhaps a mentovertex view, if the patient's condition permits. If the radiologist knew the patient had bleeding from the ears or nose, or blood in the middle ear, he would probably make additional films to

look for a fracture in some area not well visualized in the routine views. If the doctor would tell us the patient has tinnitus, unilateral deafness, or symptoms suggestive of a tumor of the auditory canal or if there is a hemorrhagic mass in the ear canal, special views could be taken.

It is not wise to speak of the radiologist reading the history and physical into the radiographs. The information is needed to enable the radiologist to plan and conduct the examination properly.

When the referring physician asks about the proper time to do a barium enema after an attack of diverticulitis with fever and tenderness, should we say 4 days after the fever is normal and the tenderness is absent? Usually this is a good rule of thumb since castor oil and enemas will not light up an infection, particularly in these days of antibiotics. It is not advisable to give enemas to patients with suspected obstruction of the bowel because evaluation of fluid levels may be difficult, and since considerable air may be introduced into the colon. Quite often intestinal obstruction, like lobar pneumonia, may not present roentgen evidence in the first few hours. Some degree of paralytic ileus may be due to hypoproteinemia when the level is below 5.5 Gm. of total protein. The inverted film of the abdomen in the newborn with the imperforate anus is best taken at 24 hours to permit gas to reach the lowermost part of the colon.

In chest studies the referring physician can be of great service by giving us information to plan our study. We must encourage him not to request a "chest plate," but to give us some pertinent facts. If we have these it will not be necessary to recall so many patients for additional views or fluoroscopy, since we will do these initially. Few radiologists would feel secure with only plain films without fluoroscopy in a child suspected of having a foreign body and in which a transitory shift of the mediastinum may be the only clue to the diagnosis. Actually we may see nothing when the watermelon seed is bouncing up and down the trachea, but the doctor may hear the slap of the seed and the Chevalier Jackson sign on auscultation over the trachea.

In an attempt to rule out or suspect an early cancer of the bronchus we need PA. films in inspiration and expiration as well as in the lateral and oblique portions and careful fluoroscopy, and then too often we have to conclude our report with, "Cancer of a bronchus may not show roentgen evidence in its early stages and can be detected only by bronchoscopy or other studies."

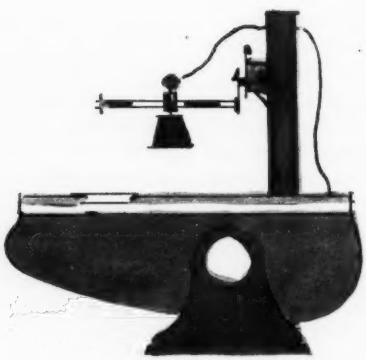
In the field of therapy, we must remember there are many doctors who have never seen or only remember vaguely the skin reactions of membrane formation, with crusts and edema, which we produce intentionally in our radiation of cancer of the skin. The complications of radiation therapy should be known by our fellow physicians. No matter how careful the radiologist may be, the fact still remains that the tolerance of normal tissue and that of cancerous tissue is very close, and with destruction of one there is danger of destroying the other, and also that individual tolerance is a variable no one can predict or explain. Why should 50% of animals or persons die from a single body-dose of say, 500 r, and yet a few will live after 800 r and a few will die after 350 r, and that there will be all degrees of variation between 350 and 800 r. Fortunately, our serious complications are infrequent and, in the treatment of a killing disease, justifiable. It is best that our doctors know these complications are not unexpected and that, if we reduce our dose to the point of no complications, we may also fail to destroy the cancer. The problem of when to tell the patient he has cancer is with us always, and books have been written on the subject. We may take for granted that the referring physician has informed the patient of this, but this is by no means always the case. By communication with the referring physician we can arrive at the best solution to what, at times, may be a difficult decision. The family physician is by far the most helpful person in our problems with cancer patients. We must have some protection and, except in the unusual case and in children, it is usually best the patient know that he has cancer. Nothing can be more embarrassing than to have a patient say, "Doctor, why didn't you tell me I had cancer? I would not have failed to report for my treatment if I had known this." Or the patient may say, "If I had known this, I would have preferred to go to the tumor clinic in a big city."

I fail to see why we need to tell the patient all of the possible complications of radiation therapy any more than the surgeon needs to detail the possible consequences of surgery.

If we do not use good judgment we may frighten the patient and have the patient stop treatment when it is essential to his life. We can tell one reliable member of the family and can also explain the situation to the patient if the patient is one who will not be frightened. No hard and fast rule can be established, and each case must be individualized. However, what surgeon says to his patient, "Some cases will have thrombophlebitis and pulmonary emboli, intestinal obstruction, wound infection, wound dehiscence, atelectasis, postoperative hemorrhage, reactions to transfusions, etc."? Let us not be so anxious to obviate every possible legal or moral blame that we do a disservice to our patient.

All doctors need to develop confidence in their fellow practitioners and we as radiologists must do everything to foster this. The problem of our charges, our willingness to reduce fees and to do charity work, should be talked over with our fellow doctors. Criticism of our department should not only be welcomed but be asked for. Our desire to be called at night or whenever needed should be expressed to them. No one knows all the answers to our problems but we will never find them if we do not start looking.

Please forgive me for such a rambling talk. I have written this paper with the hope that many of the radiologist's referring physicians will read this paper and that a better understanding of the problems will result. If someone says this paper is too much of the kindergarten type, I apologize; the paper was not prepared for the erudite.



Why Should the Practitioner Know Something About Principles of Statistics*

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Statistical methods and analyses leave the average physician "cold," and he has a feeling of complete inadequacy as he passes on quickly to "more interesting" phases of his reading. The author has done a service to the reader in his explanation of the "why and wherefore" of statistical analyses and a brief, practical review of certain principles which are not too complicated for understanding.

THIS is not an authoritative presentation. I am a doctor, not a statistician. My purpose is simple—and twofold. I will try to show that knowing some elementary statistical principles is of substantial practical value in clinical practice. Second, I will try to show that in order to take advantage of these principles it is not necessary to have a grasp of higher mathematics.

The response of the average practicing physician to even the most elementary statistical formula is often a mixture of awe and aversion. Let me try to win you to my side, then, by saying that I do not understand very well how these formulas were derived; as a matter of fact, I do not even care. If you have a sort of advanced allergy to algebra, either because of the lack of mathematical training, or because of disinterest, or because you are not very smart, the speaker is your brother.

Although mathematical methods and skills are indispensable to the science of biostatistics, from one point of view biostatistics may be thought of as a branch of the science of logic rather than a branch of mathematics. The science of statistics concerns itself with the quantitation of probability. The American institution known as Las Vegas, Nevada, is a monument to the validity and economic utility of this science.

Before I go on, let me further reassure you that I am not capable of presenting anything very complicated since I find long division difficult and, furthermore, I have no formal training whatever in either higher mathematics or medical statistics. On the other hand, my statistical mistakes have been corrected so many times in so many ways by my colleagues with professional training in statistics that I have become an authority on faulty logic.

Statistics and Clinical Medicine

Now, how do statistical principles apply in clinical medicine? In dealing with a problem in a patient, one takes advantage of a knowledge of certain medical technics, principles, and facts in gathering data which will help solve a diagnostic or therapeutic problem. In the course of performing the history, the physical examination, and the laboratory tests in a single patient, we gather many many data. Some of the data are negative, some are positive. Many of the data are quantitative, such as size of the heart, length of the history of pain, severity of cough, height of the blood pressure, etc. In evaluating these data we all make use of the laws of probability. That is to say, either consciously or "intuitively" we do apply statistical principles. The frequency with which we make the right diagnosis or apply the right treatment depends then, in part, on our skill in correctly applying the laws of probability.

Of course it does not matter whether we know we are applying statistical principles or not, so long as we come up with the right answer. The question is, how good are we at

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quantitating probability in the so-called intuitive manner which most of us employ? I do not believe we are very good at this because I have tested a number of doctors in various ways, such as by presenting certain simple problems some of which I will tell you about. These three little problems are typical of those one meets in solving clinical diagnostic and therapeutic problems. For their solution they require only the most elementary knowledge of statistical principles or logic.

Problem 1. Suppose you must decide whether or not a patient has McGoogan's syndrome. Suppose further that the most frequent manifestations of this syndrome are diarrhea (⅔ of the cases), hepatomegaly (⅔ of the cases) and skin rash (½ of the cases). In order to make the problem easier, let us also assume that the incidence of each of these three manifestations is independent of the presence or absence of the other two. You have interviewed and examined the patient and you have found that he does not have diarrhea, hepatomegaly or skin rash. You know, then, that McGoogan's syndrome is not likely, but how unlikely is it?

In order to solve the problem, all you need to know is that the chances that 2 independent findings will be present simultaneously is the product of their individual chances of occurrence. Thus, the chances that a person with McGoogan's syndrome will not have diarrhea are one in 3 (⅓); that he will not have hepatomegaly one in 3 (⅓); and that he will not have skin rash one in 2 (½). So, the chances that a patient with this condition will not have any of these findings are: ⅓ x ⅓ x ½, or 1/18. Therefore, on the basis of the evidence presented, there is only one chance in 18 that all of these findings would be absent in a patient with McGoogan's syndrome. This, of course, does not mean that he does not have the syndrome, but it allows us to quantitate specifically the available negative evidence.

Problem 2. Let us assume that our patient has McGillicudy's syndrome, which now presents us with another problem—this time in clinical therapeutics. Suppose that it is known that the mortality rate is 50% and that no effective therapy is available. Recently, as a desperate measure, you tried Mudomycin B in such a patient and were pleased to find that he survived. Subsequently, you have treated 5 additional patients with only one death. You then ask yourself whether or not the drug is really effective. In other words, how likely is it that these "good" results were due to chance alone. Since Mudomycin B is extremely expensive and moderately toxic, you do not want to continue to treat such patients unless the chances are reasonably good that a favorable effect is being exerted. In order to weigh properly this factor against the disadvantages of this therapy, it would be highly desirable to measure quantitatively the likelihood that a beneficial effect has really occurred. What then are the chances that 5 of 6 would have survived if no therapy were given? Well, we know that without therapy in each patient there is one chance in two of survival. We also know that there is one chance in 64 (½ x ½ x ½ x ½ x ½ x ½, or 1/64) that the results will occur in any specific order, such as 5 survivals followed by one death. Furthermore, we can assume that any one of 6 possible situations would satisfy our criterion of 5 of 6 survivals. In other words, the single death would have occurred in the first, second, third, fourth, fifth, or sixth case. It follows then that the chances that 5 of 6 will survive are 1/64 + 1/64 + 1/64 + 1/64 + 1/64 + 1/64, or 6/64. Therefore, the chances that the "favorable" results were due to chance alone are about one in eleven.

Problem 3. One type of problem frequently encountered in clinical medicine is one in which it is necessary to determine the probability that some particular combination of circumstances is or is not significant. The sample problem stated below is not a medical one, but the elementary logic or elementary statistics required for its solution are quite similar to those required in the solution of certain diagnostic problems.

Suppose there are 30 people at a birthday party and a discussion arises as to the chances that any two individuals in the room have, by coincidence, the same birthday. Are the chances one in 30? One in 10? Or one in 5? It is logical to assume that the chances that any two persons have the same birthday are one in 365. Thus, the answer can be easily derived by determining the number of possible pairs at the party, for which there is an appropriate formula. However, it is not necessary to know this formula, since one can proceed by very elementary logic. We know that

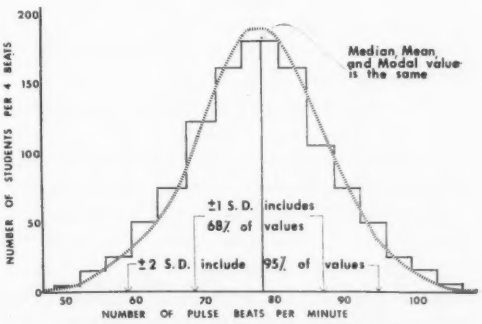
person number one could be paired with any of 29 individuals. Person number two has already been paired with person number one, but there are 28 others with whom he could compare birthdays. Thus, the number of possible pairs is 29 + 28 + 27, etc. Now, add up all possible pairs and you will find that there are 435 possible pairs in the group (as compared to only 365 days in the year). It follows that the chances are somewhat greater than "fifty-fifty" that two individuals in the group will have the same birthday.

If one asks a series of physicians to solve these elementary problems one gets a discouragingly wide range of answers, indicating that most doctors are not very good at applying their so-called intuitive thinking to the solution of "diagnostic" problems involving quantitation of probability. Yet, being able to quantitate probability in this way is of great practical value. We recognize that this is so when we attach importance to knowing what the mortality rates are in connection with certain surgical procedures. Knowing whether the mortality rate is 10% or 30% does not allow us to predict which patients will die, but it allows us to weigh quantitatively the probability of surgical mortality against the risk of nonsurgical management. Thus, error cannot be eliminated but it can be minimized. Whether one consciously uses statistical formulas or not, one must use statistical principles (quantitative logic) to be effective. Those of us with a distaste for statistical expressions and mathematical formulas ought to admit the practical importance of statistical principles in clinical practice. Furthermore, we should carefully evaluate whether we are really as good at quantitating probability as we ought to be.

The application of the laws of probability in distinguishing between normal and abnormal values. One of the most important problems in medical practice is the problem of distinguishing the normal from the abnormal. Everyday we are required to decide whether symptoms, signs, or tests are or are not normal. Usually we divide findings into 4 approximate categories. We find that they are either: definitely normal, possibly abnormal, probably abnormal, or definitely abnormal. When we deal with findings which are of a borderline character, which is quite frequent, it is very helpful to be able to express quantitatively the probability of abnormality. For example, are the chances of abnormality one in 2 or are they one in 10? By employing certain elementary statistical principles it is sometimes possible to determine more precisely this degree of probability. To do this we must be aware of the relative frequency with which various normal (or abnormal) values occur.

A so-called frequency-distribution curve is presented in figure 1. If one selects a series of normal individuals at random and performs some kind of test or measurement on each of them, the results often are distributed in this way with respect to frequency. For example, when pulse rates of healthy medical students were determined by Bancroft,[1] it was found that the average pulse rate was 77 beats per minute and also that this particular rate occurred more frequently than any other rate. This "peak" incidence value is called the modal value. Rates within two to ten beats per minute higher or lower than the modal value were frequent, but little less frequent than values which were even closer to the modal value. Rates progressively farther from the modal value were progressively less frequent. By determining pulse rates in many hundreds of these students and plotting the results, this frequency-distribution curve was obtained from which the degree of inter-individual variability of the pulse rate could be determined. On the other hand, it is possible to estimate the expected variation in an easier way. One can measure the pulse rate in a much lesser number of individuals, say 50, *who have been selected at random* from a

FIG. 1



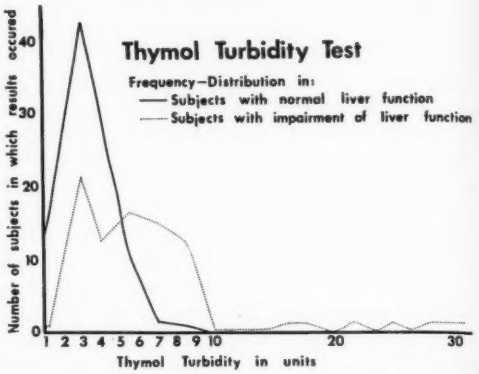
The resting pulse rates of medical students (data of Bancroft[1]). The frequency distribution is shown graphically. These values distribute themselves in a "normal" fashion. See text for discussion.

larger group. It is then possible to apply a formula to derive a number which will permit a fairly satisfactory estimate of the degree to which normal pulse rates might be expected to vary. This measure of variation is called the Standard Deviation. We will not interest ourselves in the formula used to derive the Standard Deviation, but let it suffice to say that about 68% (⅔) of the values can be expected to be within one standard deviation (plus or minus) of the mean average value and that 95% of the values in a particular group may be expected to lie within two standard deviations of the mean. Knowing this, one can then calculate the probability that any certain value is normal in a manner which will be indicated subsequently. It should be apparent that these data from a selected population group (students) are not necessarily completely applicable to other groups, for example, elderly individuals or athletes.

Normal values are distributed so often in the manner shown in figure 1 that frequency-distribution curves of this configuration are called "normal" curves. To some extent this is unfortunate since some groups of normal values do not distribute themselves in this configuration. Normal frequency-distribution curves are sometimes called "Gaussian" curves after the man who described this phenomenon. It should be noted that when normal results are distributed in this way the mean (average) value is the same as the modal (most frequent) value and both are the same as the median (central or middle) value. On the other hand, this is not true of all measurements in groups of normal subjects. For example, the mean, modal, and median values were all slightly different when normal individuals had thymol turbidity tests, since the data were distributed in a somewhat assymmetrical manner (Fig. 2).

The data in figure 2 are shown to illustrate how one can make practical use of a frequency-distribution curve. We see that when subjects without liver disease were tested by Zieve and Hill[2] with a thymol turbidity test, almost all of them had values less than 6.5 units (mean of 3.2 units). On the other hand, most of the subjects with proven liver disease had values above 6.5 units (mean of 7.9 units). It is apparent, however, that there is a large overlap between the values in individuals

FIG. 2

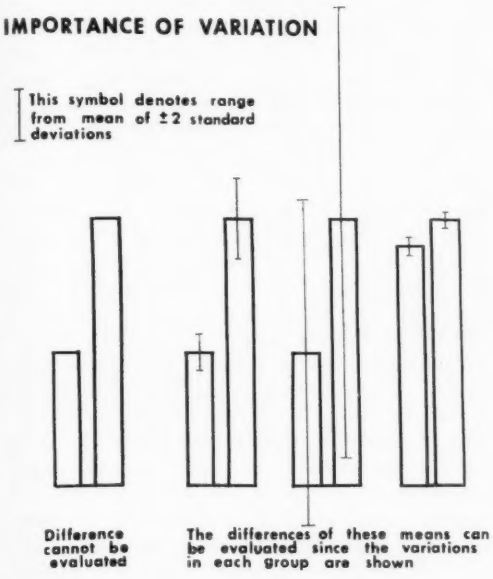


These data are those of Zieve and Hill.[2] (See text for discussion.)

with and without liver disease. The important thing to note, however, is that if one knows the frequency-distribution curve of both the normal and abnormal values, one can derive the probability of normality (or abnormality) of any given value. For example, although the value of 7 units occurs in both normal and abnormal individuals it is several times more common in persons with abnormal liver function. Similarly, although a value of 3 units may occur in subjects with abnormal liver function, it occurs about twice as frequently in normal individuals. Thus, by having a mental image of the frequency-distribution curves of clinical values, one usually can make some use of a result even when it falls into the so-called overlap or borderline range.

The importance of knowing variation in interpreting the significance of differences. In figure 3 on the far left are shown a pair of bars which represent the mean or average results in two different groups. Suppose these results represent the responses of subjects with and without Cushing's syndrome to a new test. The mean value is twice as great in those with Cushing's syndrome. This difference may seem impressive, but there is no way to evaluate its significance until one knows the variation of the individual results in each of the two groups. Suppose, then, that we measure this variation by determining the standard deviation of the results in each group. We then indicate this variation in the usual way, by placing a vertical line along the center of the bar extending for a distance of two standard deviations above and below the mean. If

FIG. 3


IMPORTANCE OF VARIATION
This symbol denotes range from mean of ±2 standard deviations
Difference cannot be evaluated
The differences of these means can be evaluated since the variations in each group are shown

See text ("Importance of knowing variation") for discussion.

the results conform to those represented by the pair of bars second from the left, it is apparent that almost all of the values in patients with Cushing's syndrome are outside the normal range, confirming that the two groups are, indeed, quite different. On the other hand, on examining the variation we might have found the results depicted by the third pair of bars. In this case, although the average of one group is twice as high as the other, the deviation in each group is so great that there is a wide overlap of the values in the two groups and they may or may not be significantly different. At any rate, the test would not be very helpful in Cushing's syndrome. The last pair of bars on the right in figure 3 depict additional theoretical results in two different groups. Here we see that the mean results are quite similar. On the other hand, the variations are so small that even this small difference in the mean is significant, and therefore, possibly of clinical value.

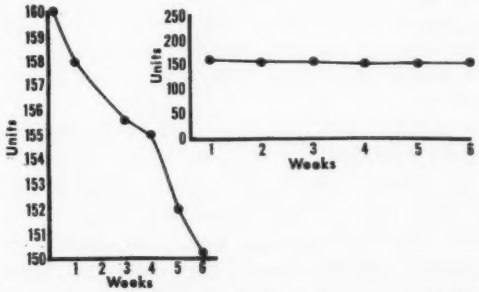
Data may be presented in a misleading fashion. Probably too much has been made of the fact that statistics may be misused. Yet it is true that a great many examples of errors in presenting, analyzing or collecting data might be given. However, let it suffice to say that one of the most frequent errors made by clinicians and investigators is in adopting controls which are not really suitable. For example, the glucose tolerance tests of normal young adults are often used as "controls" in deciding whether or not an elderly patient has diabetes.

There is one other interesting example of the misuse of data which I would like to mention. This concerns the practice of presenting data in an accurate but misleading way. In figure 4 the same data (exactly) are presented in two different ways. Author A presents the data shown on the left. By arbitrarily adopting suitable horizontal and vertical scales he presents a graph which appears to show an impressive and precipitous drop in the blood porcelain level. On the other hand, his antagonist, Author B, presents exactly the same data (right portion of figure 4) in such a way that the values appear not to change at all. Both presentations are "accurate," it is up to the reader to be alert to this technic of "scalesmanship" by which one may fool others or himself.

Other Common Statistical Expressions and Technics

When are results statistically significant? Before closing, I would like to review very briefly the meaning of a very few statistical expressions which appear frequently in the medical literature. One frequently sees the expression "statistically significant" or "not statistically significant." Unfortunately, if no further explanation is given the meaning may be vague. What is usually meant is that some sort of analysis has been performed to determine the degree of likelihood that one

FIG. 4



These are two different graphs of exactly the same data. One appears to show a precipitous drop in blood porcelain levels, while the other appears to show an impressive lack of change. This dramatizes the evil potentialities of the art of "scalesmanship."

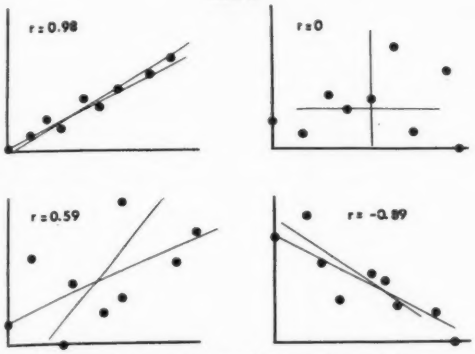
group of figures is different from another. By custom, if an observed difference would have occurred on the basis of chance in one of 5 or 10 instances, a difference is not considered to be "statistically significant." On the other hand, if chance alone could have accounted for the difference in only one of 20 or more instances, the difference is usually considered to be "statistically significant." The degree of likelihood that the difference between the two groups can be explained by chance alone is expressed by using what is called a "p" (for probability) value. For example, if p is .05 (or 1/20) there is one chance in 20 that this difference could be explained on the basis of chance alone. When p is .01 (or 1/100) there is only one chance in 100 that there is not a real difference. It should be remembered that even if the p value is impressive, say .01, this does not prove anything. For example, if a group of patients are significantly (p of .01) better after a period of treatment with a drug than another group receiving no drug, the apparent difference in result is not necessarily due to the drug. It could be due to the psychologic effect of the administration of the drug. It could be due to the fact that the two groups of cases studied were not alike initially or, lastly, it could be due to the fact that one of many investigators who tried the drug observed these results on the basis of chance alone. Of course the person with results which are apparently more "favorable" is the most likely to publish a paper. Conversely, the fact that a difference between two groups of figures is not statistically significant does not necessarily mean that a difference does not exist, particularly when the number of observations is small. For example, the difference between a mortality rate of 30% and one of 60% might be statistically insignificant if there were only a few cases in each group. Further observations might reveal a highly significant difference or no difference.

What is the t test? One of the most frequent ways employed to find out how likely it is that chance alone will explain a difference is by using a method called the "t" test. This test is not appropriate unless the data meet certain specifications. For example, both groups of data have to be distributed in a so-called normal fashion and the degree of variation in each group must be about the same. Nevertheless the t test is frequently used, sometimes appropriately, sometimes inappropriately. The formula is applied to the data and a so-called t value is derived. One can then look in a table and derive a p value which will show how likely it is that chance alone could explain the difference observed.

What is the chi square test? Another procedure frequently mentioned in the medical literature is the chi square test. This test is often useful in comparing incidences. For example, suppose 15 of 50 patients (30%) are cured when a certain method of treatment is used and 9 of 20 (40%) are cured when another type of therapy is employed. By using the chi square analysis, one can determine the probability that such a difference might occur if the treatments were equally effective. You do not have to know how to derive the formula; you do not even have to know the formula. All you need to know is that it is available and that it is applicable in this situation. Then, if you want to know whether your own results or your colleague's results are "significantly" better, or not, you just look it up in a book or consult a medical statistician who will help you. (Nothing is more fun than analyzing the data of someone you dislike and finding that his apparent differences were not really significant or that he used the wrong test.)

What is the correlation coefficient? The last technic of analysis I will describe is the correlation coefficient. This procedure is used frequently for the purpose of determining how likely it is that a relationship exists between two entities. A formula is employed in comparing two sets of figures. When a perfect relationship exists (such as between the weight in pounds with the weight in kilograms) then the so-called "r" value is 1.0. If no relationship exists, the value will be zero or near zero. If a negative relationship exists which is perfect (such as the relationship between pleasure and paying income tax) the r value will be −1.0. The relationship between two groups of paired figures can be easily "visualized" by plotting the data in a graphic way (Fig. 5). When the plots fall in line, it is apparent that a relationship exists. On the other hand, when they are scattered about with no tendency toward line formation no correlation exists. If a moderate but incomplete relationship exists (such as between height and weight)

FIG. 5



These theoretical examples are from the book of Snedecor.[3] They show that the correlation between two groups of figures can be estimated "visually" by plotting the results graphically. (See text for discussion.)

the r value would be between 0.3 and 0.7. It should be mentioned, however, that a relationship may change as one value or another reaches a certain level. The manner in which these latter "non-linear" relationships are handled is beyond the scope of this discussion. However, this is a good example of the possible limitations of a physician who may know a little about statistics and his dependence at times on a professional biostatistician. In figure 5, several theoretical examples taken from Snedecor[3] illustrate the relationship between the actual r value for coefficient of correlation and the geometric configuration of the plots.

The illustration at the bottom right of figure 5 could well describe the almost completely negative relationship (—0.89) between the length of a Chairman's Address (horizontal axis) and the enthusiasm of his audience (vertical axis). This would not prove that it would be wise to end the Address, but examination of appropriate statistical tables would show that there is less than one chance in a hundred that it would be advisable to continue.

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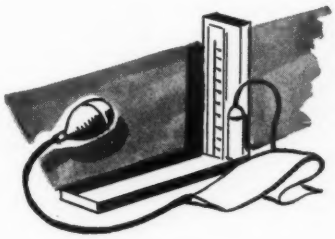

Treatment of Tinea Versicolor

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The author believes this combination of an acridine and hexylresorcinol are efficacious in the treatment of this fungal skin disease.

TINEA VERSICOLOR, a benign, noncontagious superficial fungus infection caused by *Malassezia furfur* appears as a macular eruption on the upper trunk and shoulders most frequently. The lesions may be pink, light tan, or depigmented areas. Both discrete and confluent lesions are commonly seen in the same patient.[1] Although the condition is most commonly observed during the summer, many cases are also seen during the cooler months of the year. Subjective symptoms are usually absent but occasionally mild itching occurs, particularly those who sweat profusely.

Many preparations have been used in treatment with varying degrees of success over the past 100 years. Drugs as sulfur, salicylic acid, a combination of sulfur and salicylic acid, resorcin alone and in combination with other drugs, saturated solution of sodium thiosulfate, tincture of iodine, and mercuric chloride have been partially effective, ineffective or sensitizing in the vast majority of patients treated. Robinson and Yaffe, proved the effectivity of selenium sulfide in the treatment of 32 patients with tinea versicolor.[2]

During the past year Akrinol has been used in the treatment of 38 patients with tinea versicolor. The results of this study form the basis for the following report.

Method of Study

The drug. Akrinol is a chemical combination of 9-aminoacridinium and 4-hexylresorcinolate. The acridines, of which 9-aminoacridine is a member, have seemed to exert a bactericidal or bacteriostatic effect upon a variety of organisms.[3] Hexylresorcinol has been used as a urinary antiseptic since 1924,[4] as an anthelmintic since 1931,[5] and has also been described as an efficient antiseptic when applied locally.[3]

The combination of drugs is a yellow crystalline compound which was used as a cream containing 2 mg. per Gm. in a water miscible base, and as an aerosol spray containing 10 mg. in each 150 Gm. dispenser. The preparations are free of odor and pharmaceutically acceptable.

Case selection. The patients included in this study were ambulatory and were treated in the dermatology outpatient department of the University Hospital and in the author's private practice. The patients ranged in age from 15 to fifty-eight. There were 4 negro males, 3 negro females, 16 white males and 15 white females.

Treatment. The microscopic diagnosis of tinea versicolor was established in all patients by the use of 20% hydroxide preparation or the ink-KOH stain before therapy.

Patients were instructed to shower with warm soapy water each morning, and to thoroughly rinse with clear water to remove all traces of soap, then to pat the skin dry with a towel. Towels and all clothing worn next to the skin were to be laundered in hot soapy water, thoroughly rinsed and dried before being used again.

The 12 patients who used the aerosol spray containing Akrinol were advised to hold the spray can 12 inches from the skin and to spray the areas involved twice each day until the surface was lightly moist. The 26 patients who used the cream were instructed to apply a thin film of the medication twice daily to all affected areas. Patients were advised to have some assistance at home in applying the medication so that all inaccessible areas would be treated. Applications were continued for 2 weeks and then terminated. Patients were observed weekly for the first 2 weeks and then at 3 week intervals.

Those who used the aerosol spray used on an average of 3 cans in the 2 week period; those who used the cream used an average of

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Supplies of Akrinol used in this study were supplied by Dr. Edward Henderson and Dr. G. K. Hawkins of the Schering Corporation, Bloomfield, N. J.

4 tubes during the 2 week period. The amount of medication used varied with the extent of the eruption.

Results

Thirty-six of the 38 patients treated with Akrinol spray or cream obtained an excellent result with complete clearing of the lesions within 4 to 8 weeks after the initiation of therapy. Two patients who failed to respond to treatment with the spray showed a satisfactory response when the cream was applied. Recurrences were noted in 5 patients after a period of 3 months but all of these responded to a second course of treatment. No adverse reactions were encountered.

Comment

The results obtained in this study and those reported by Zimmerman[6] and Reiss[7] indicate that Akrinol is specific in the treatment of tinea versicolor. The value of this preparation is enhanced by the fact that it is pleasant to use, free from unpleasant odor, and nontoxic. The lack of adverse reactions also indicates its superiority to other preparations in the treatment of this condition.

Tinea versicolor is a very common dermatosis. Although the condition is not productive of subjective symptoms, as a general rule the cosmetic defect caused by this condition is particularly embarrassing during the summer months when bathing suits or other brief clothing are being worn. It is of great value to the practitioner to have available a preparation which is effective and free from annoying adverse reactions.

Tinea versicolor is prone to recur regardless of the treatment used, and the experience with Akrinol is not sufficient to indicate whether it will eradicate the condition and prevents its recurrence. Therefore, it is suggested that the treatment with this medication be used for 4 weeks after the lesions have disappeared and microscopic examinations are negative.

Conclusions

1. Akrinol has been used in the treatment of 38 patients who had tinea versicolor.

2. It was used as an aerosol spray in treating 12 patients and as a cream in 26 patients.

3. Satisfactory results were obtained in all patients in from 4 to 8 weeks.

4. Recurrences in 2 patients were satisfactorily treated with re-application of medication.

5. No adverse reactions were encountered.

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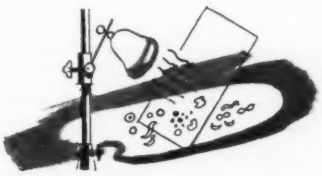

Clinical Evaluation of Parenteral Hydroxyzine for Preoperative Medication

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The search for better medication preliminary to anesthesia continues. The authors believe this ataractic drug has certain assets which may offer advantages in premedication.

Introduction

CLINICAL INVESTIGATION of a psychotherapeutic agent, hydroxyzine hydrochloride,* as preoperative medication has been carried out at the Lloyd Noland Hospital for the past 2 years. This investigation was undertaken since hydroxyzine, a drug used clinically in medicine for 4 years to produce ataraxia, was found to possess many pharmacologic properties which are conducive to a smooth anesthetic course. It was thought that such a drug, which purportedly produces peace of mind without depression of vital functions, would be a valuable adjunct to the anesthesiologist. Thus it was decided to study the effects of parenteral hydroxyzine for preoperative medication and to note effects on vital functions. Careful observation was made to note the occurrence of any side-effects.

Chemistry, Pharmacology and Clinical Use

Hydroxyzine HCl is a parachlorobenzhydryl piperazine derivative which has been shown to have antihistaminic, antisecretory and antiarrhythmic properties. In experimental animals the compound reduces spontaneous motor activity, antagonizes the emetic effect of apomorphine, and protects the myocardium against arrhythmias induced by epinephrine.[1,2]

Clinically, hydroxyzine has been reported to be a useful calming agent in all age groups.[3,4] It has been successfully used in the management of acute alcoholic intoxication and certain cardiac arrhythmias.[5,6] Its use in general anesthesia has been reported in Italy.[7] No serious side-effects seen with drugs used similarly, such as hypotension, jaundice, extrapyramidal symptoms or blood dyscrasias or any contraindications to its use have been reported.[8-11]

Method

Hydroxyzine has been used as preoperative medication in over 1,000 patients. In 400 unselected patients, a careful study of the response to the drug was made by one of us (A.L.R.) who completed a detailed form summarizing the results in each case.

A preoperative anesthesia history was obtained and a physical examination was done on each patient. During the preoperative visit the anesthesiologist attempted to engage the patient in a discussion of his fears concerning anesthesia and surgery, and supplied whatever explanation and assurance that seemed necessary. Suitable medication was prescribed one hour prior to operation, consisting of hydroxyzine, ranging in a dose of from 25 to 100 mg., and in most cases atropine and one half the calculated therapeutic dose of meperidine combined in the same injection. Children were given as premedication, hydroxyzine 1 mg. per pound, meperidine, 0.5 mg. per pound and scopolamine .05 mg. per 10 pounds.

During the course of anesthesia and in the recovery room, hydroxyzine was given intravenously when indicated or when specific drug responses were being studied.

In addition to careful appraisal upon arrival in the operating room, during anesthesia, and in the recovery room, patients were observed carefully for at least 5 days postoperatively.

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*Hydroxyzine hydrochloride was supplied as Vistaril by Pfizer Laboratories, Division of Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

TABLE 1

AGE DISTRIBUTION

0-10	18
11-20	47
21-30	38
31-40	87
41-50	96
51-60	63
61-70	34
71-80	14
Over 80	3

Results

Tabulation revealed that patients were of both sexes in almost equal numbers. In table 1 is shown the distribution according to age ranging from 4 to 91 years. The greatest number were in the 30 to 50 years group, with 51 patients in the over 60 group.

In table 2 is given the case distribution as related to the region of operation. It includes all except obstetric patients.

Table 3 lists the principal anesthetic used with the number of patients having postoperative nausea. The incidence of postoperative nausea in unselected patients having as premedication meperidine and atropine, and given anesthesia by the same individual was 10% as compared with 5.5% in this series.

Early experience showed that low doses of hydroxyzine failed to produce the desired level of psychic preparation. When given one half the therapeutic dose of meperidine and hydroxyzine in from 25 to 100 mg. dosage (averaging 75 mg.) in adults, patients arrived at the operating room dozing lightly or in a wakeful state. In 98% of patients it was thought that proper psychic preparation was achieved. A condition of cooperation, quietness and emotional stability, without undue apprehension, anxiety, fear or depression, was the criterion by which proper psychic preparation was adjudged.

TABLE 2

OPERATIVE PROCEDURE BY REGION

Intradural	2
Extradural	2
Head, neck	36
E.N.T.-Endoscopy	10
Intrathoracic	3
Extrathoracic	22
Abdomen, upper	35
Abdomen, lower	69
Genitourinary-gynecologic	87
Extremities	77
Other	57

TABLE 3

PRINCIPAL ANESTHETIC WITH INCIDENCE OF POSTOPERATIVE NAUSEA

	Number	*Nausea*
Thiobarbiturates	139	4
Cyclopropane	64	7
Fluothane	17	1
Ether	10	2
Spinal (without supplement)	61	2
Spinal (with supplement)	98	6
Caudal and epidural	8	0
Brachial blocks	2	0
None	1	0

No significant uniform elevation or diminution of pulse rate or blood pressure occurred in this series. Three patients who had clinical evidence of moderate preoperative depression had received the full therapeutic dose of meperidine and scopolamine with 100 mg. of hydroxyzine. No clinically detectable depression of the respiration or circulation occurred secondary to parenteral hydroxyzine.

The patients who had satisfactory psychic preparation underwent induction with ease. As a rule there was smooth maintenance of anesthesia and usually rapid recovery. Two patients had a short period of delirium upon emergence.

Of 81 emergency patients in this series, 10 were under the influence of alcohol in varying amounts. These patients were given premedication with hydroxyzine and atropine with uniformly good results. Emesis upon induction and emergence was absent in all these patients.

Table 4 summarizes the salient results of the study. Striking are the absence of hypotension and respiratory depression attributable to hydroxyzine. Only 8 patients were judged to have had an inadequate effect from premedication. No untoward side-effects have been detected secondary to hydroxyzine medication.

TABLE 4

RESULT OF STUDY

	Number	*%*
Poor preoperative effect	8	2.0
Depression of the central nervous system, preoperative	3	.7
Preoperative nausea	3	.7
Hypotension during anesthesia	0	
Respiratory depression	0	
Postoperative nausea (immediate)	22	5.5
Emergence delirium (mild)	2	.5

Discussion

It is possible that the use of a psychotherapeutic agent in premedication may lead to a new concept in the preoperative preparation of patients. In this era of conduction anesthesia and agents for general anesthesia which afford induction almost without psychic or physical trauma, patients can enter the operating room suite with their mental and physical processes functioning at a normal homeostatic level. The concept of amnesia as a necessity for premedication definitely is being challenged, for the positive psychic advantage of an agreeable recollection is more profitable than an absence of memory. Elimination of the mysticism associated with surgery and anesthesia will lead to ultimate benefit for both physicians and laymen.

Just as the use of deeper planes of general anesthesia has been abandoned in the interest of maintaining normal physiologic mechanisms, so the use of depressant drugs for premedication, which produce the all too common uncooperative "hypotensive mummies," should be discontinued. It is believed that the term "hypotensive mummy" best fits the impression one gets of a patient with too much premedication by potent cortical and medullary depressants, and who arrives in the operating room unresponsive, unconscious and with hypotension.

Summary and Conclusions

1. Proper psychic preparation was produced by hydroxyzine in 98% of the patients studied. Cortical effect, that is quiescence, was present rather than deep medullary depression or hypnosis. Hydroxyzine fulfills this aim rather than producing "hypotensive mummies" which are produced by other drugs.

2. The incidence of postoperative nausea was 5.5% compared to 10% in the control group.

3. Absence of side-effects.

(a) There was no evidence of respiratory depression preoperatively or following intravenous hydroxyzine in 25 to 100 mg. doses during anesthesia.

(b) Hypotension attributable to hydroxyzine in general or conduction anesthesia, was not produced preoperatively or during anesthesia.

(c) Jaundice, extrapyramidal symptoms or other side-effects were not observed with hydroxyzine.

4. In the preparation of patients in acute alcoholism, parenteral hydroxyzine in 50 to 100 mg. doses produced a quieting effect without the depression observed with other drugs. All 10 patients with acute alcoholism in this series became cooperative and none had postoperative nausea or emesis in the immediate postoperative period.

5. Absent local irritating effect. Intravenous or intramuscular hydoxyzine produced little burning or discomfort on injection. There was no evidence of vasospastic phenomena following intravenous hydroxyzine. No thrombophlebitis or fat necrosis occurred secondary to intramuscular hyroxyzine.

6. Variable dosage requirement. The dose of hydoxyzine required to produce the desired degree of psychic preparation was variable. Additional doses could be given as required without producing hypnosis or medullary depression.

7. It is believed that further investigation into the use of psychotherapeutic drugs by the anesthesiologist is warranted, and that the new concepts of premedication discussed herein should be considered as a more direct and positive approach to the problem.

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Management of Lymphoma Cutis with Low Megavolt Electron Beam Therapy: Nine Year Follow-Up in 200 Cases*

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The authors point to the highly satisfactory palliative effect of this relatively new physical means of therapy. This represents a new modality applicable in malignancy especially of cutaneous distribution.

OVER THE PAST NINE YEARS low megavolt electron beam therapy has been the mainstay of treatment for patients with cutaneous lymphoma. This study began in August 1951, and now includes an experience with 200 consecutive cases of lymphoma cutis (mycosis fungoides).[1] This paper will report our experience in the management of these patients, particularly with reference to the use of directed streams of electrons with controllable energies in the 1 to 4 million volt range. This application of electrons in total body surface irradiation has been found to be uniquely suitable for the treatment of radiation-sensitive disease which includes the extensive superficial malignant lesions seen in lymphoma cutis.

In spite of the number of patients reported in this series, mycosis fungoides is not a disease entity of increasing frequency. In many instances, however, it is being recognized and treated earlier in its course. The disorder was first named by Alibert, in 1832, to distinguish a peculiar widespread skin disease characterized by an often prolonged erythematous or eczematous phase, which ultimately gives way to infiltrated plaques and tumors. The course is prolonged and usually fatal. The disease is more common after the age of 40; in this series the diagnosis was made in 27 of the 200 patients before the age of 40. Males predominate 2 to 1.

In many patients the disease follows a pattern which is clinically distinguishable. The first is the premycotic or erythematous phase; this often merges with the second or infiltrative plaque stage and finally the third or tumor stage. Overlapping is common and all three stages may be seen in the same patient. Itching is intense in all three stages. The course is variable and differs from patient to patient. Remissions may occur in any phase. Most writers, however, are agreed that the prognosis in the tumor stage is measured in months, and most textbooks state that patients in the third stage of the disease usually die after two years. The disease appears to originate in the skin in multiple foci and runs its course predominantly in the skin. As is common in the lymphoma group, the disorder may revert to a more malignant and rapidly fatal form of the disease with a histologic picture resembling lymphoblastic or, more commonly, reticulum cell lymphoma (sarcoma). This is usually a terminal event and the histologic appearance of the infiltrate of many organs closely resembles the microscopic findings in the skin.

Unfortunately, accurate diagnosis in the erythematous first stage of the disease is often histologically and clinically impossible. The eruption may mimic widespread eczema,

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scattered patches of psoriasis or parapsoriasis, or exfoliative erythroderma. The appearance of this type of eruption, which has persisted in spite of good management, in a middle-aged individual should make the physician suspect the premycotic stage of mycosis fungoides. In the plaque stage the lesions are pink to deep red, usually well circumscribed, and have circular, irregularly cyclic, or gyrate borders. In the third stage the tumors are brown to reddish purple, of variable size, and dome-shaped, and many undergo spontaneous ulceration. Widespread lymphadenopathy may be seen but on histologic study of nodes a report of dermatopathic lymphadenitis usually is made. In 5 of our patients a picture of poikiloderma atrophicans vasculare was presented many months and years before any type of ionizing therapy was begun. Although the histologic diagnosis of mycosis fungoides is consistently made in the plaque and tumor stage, it should be emphasized that multiple biopsies are helpful in any stage of the disease.

Because of the expected fatal outcome in patients suffering from mycosis fungoides, many conservative and indeed heroic methods of treatment have been used in the past. Spot treatment with superficial x-ray therapy of conventional quality has sufficed for isolated lesions which are usually radiosensitive. Spray therapy with various qualities of ionizing radiation has been effective in some instances. Chemotherapeutic agents of a wide range of activity, from arsenic and tartar emetic to established and experimental cytotoxic agents, have been used. Nitrogen mustard has often produced dramatic benefit but the results are short-lived. Steroids and other anti-inflammatory agents, such as antimalarials, have been effective in the early stages of this disorder so that actual treatment with ionizing radiation may be delayed for months in some instances. Localized plaques have responded to strontium-90 applications, intralesional injections of steroids and direct applications of nitrogen mustard to the tumors. The relentless progression of the disease toward the infiltrated plaque and tumor stage, however, ultimately demands a modality that suppresses the disease in the skin which is apparently its site of origin. This can best be accomplished by total body surface irradiation with the electron beam, with adjunct treatment dictated by special circumstances and individualized to the patient.

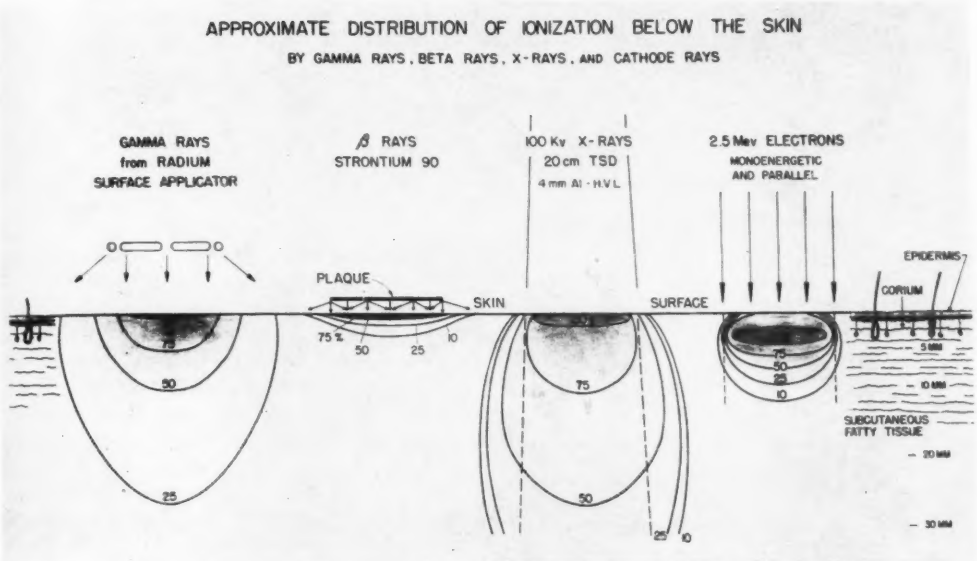
Methods and Materials

Patients subjected to total skin surface irradiation with electrons presented multiple or extensive lesions of mycosis fungoides involving almost all of the cutaneous surface. Over 90% of these patients had been subjected to many of the conventional methods of treatment already enumerated. Superficial x-ray treatment with conventional methods is time-consuming. There are the additional factors of radiation damage and depressing effects on the hematopoietic system with this modality. The highest degree of ionization is delivered at the skin surface with conventional x-ray therapy. Furthermore, when the dosage of radiation is high over large body surfaces, depression of the bone marrow may result, followed by pancytopenia. Moreover, with doses required for cutaneous malignant lesions the danger of irreversible changes in the bone marrow is inevitable. Many of these difficulties may be obviated by the use of electron therapy. Electrons in the low megavolt range have the unique quality of limited penetration and also some degree of skin-sparing effect.

In this study the source of electrons was obtained from a constant-potential electrostatic generator of the Van de Graaff type insulated in compressed gas. The electron beam emerges into air from the evacuated acceleration tube through an aluminum window of 3 mil thickness. The generator was housed in the Department of Electrical Engineering of the Massachusetts Institute of Technology. It can be shown by suitable measurements that the maximum ionization of the electron beam lies a few millimeters under the skin surface, depending upon the accelerating voltage. Electrons can be accelerated by voltages controllable from 1.5 to 4.0 million volts and the depth of penetration is in direct proportion to the voltage applied at the source. Lesions of the plaque and tumor stage of mycosis fungoides generally require more deeply penetrating electrons (Fig. 1).

The skin-sparing qualities of the electron

FIG. 1



Dose distribution below skin produced by gamma rays from a surface applicator, beta rays from a contact plaque of strontium-90, 100 kv. x-rays at 20 cm. T.S.D., and 2.5 Mev. monoenergetic parallel electrons approaching perpendicularly. (From Wright et al., Radiology, October 1956.)

beam are demonstrated by the following example. When electrons are produced at 1.5 million volts at a distance of 122 cm. from the exit window to the area of treatment, the entrance or dosage at the skin surface is approximately 80% of the maximum with the highest dosage 1.5 mm. under the skin surface. Table 1 shows depth dosages of electrons as the voltage varies.

Since ionization is almost totally absent beyond the maximum electron range, depression of the bone marrow does not occur and vital organs are not affected. Cyr[2] reviewed the hematologic changes in the first 40 patients in our series. In 75% of the cases no blood changes resulted except for transient lymphopenia. Varying degrees of bone marrow depression were found in 25 per cent. After modifications in the original apparatus, no discernible bone marrow depression has been noted in the following 160 patients in this series.

TABLE 1

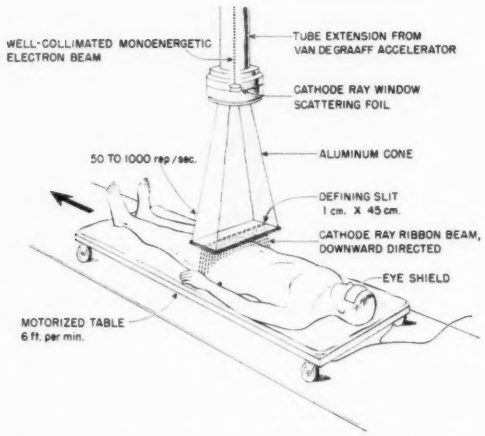
DEPTH OF DOSE IN RELATION TO ELECTRONS OF VARIOUS VOLTAGES

Electron energy (Mev.)	1.5	2	2.5	3	3.9
Depth of dose—maximum (mm.)	1.5	2	3	3.5	5
Depth of 50% of dose —maximum (mm.)	3	5	7	10	12
Maximum depth (mm.)	6	9	12	15	20

Electron therapy has a high inherent efficiency as contrasted with x-ray therapy. All the energy of the electrons incident on the patient is locally absorbed and is biologically as effective as x-rays. Likewise, for physical reasons electrons of high energies fortuitously favor the radiosensitive skin layers and permit a build-up of ionization to a peak value below the skin surface. Since electrons have biologic activity similar to x-rays, all precautions which govern the use of x-rays also apply to the use of electrons.

The procedure for total body radiation with electrons is shown in figure 2. The patient is placed on a motorized platform under the slotted aluminum cone so he may receive a nearly uniform dose of electrons over a large body surface. The output of the electron beam is adjusted so a single traverse from head to foot requires less than one minute. During this time the generator is regulated to deliver 200 rad entry dose to all exposed skin. In an initial course of treatment, the anterior and posterior surfaces are treated

FIG. 2


WELL-COLLIMATED MONOENERGETIC ELECTRON BEAM
TUBE EXTENSION FROM VAN DE GRAAFF ACCELERATOR
CATHODE RAY WINDOW SCATTERING FOIL
50 TO 1000 rep / sec.
ALUMINUM CONE
DEFINING SLIT 1 cm. X 45 cm.
CATHODE RAY RIBBON BEAM, DOWNWARD DIRECTED
EYE SHIELD
MOTORIZED TABLE 6 ft. per min.

Electron cone in position, with patient on motorized table. (From Wright et al., Radiology, October 1956.)

one day, and the lateral surfaces are exposed on the second day. The tangential skin surfaces are protected to prevent overlapping of the treated areas. The eyes and scrotum are shielded with sufficient thickness of cloth-covered metal, plywood, rubber, or some other low-atomic-numbered absorber. Uninvolved areas can be similarly shielded. Thus, six treatment days are required to bring the entry dose level over the entire skin surface to 600 rad—the total dose commonly used in the initial treatment of mycosis fungoides. Recurrences are treated by protecting uninvolved areas and applying a dose of 400 rad at a single exposure, or 300 rad on successive days to a total of 600 rad.

Clinical Data

Since 1951, we have treated 200 patients with mycosis fungoides. The geographic distribution of these patients is shown in table 2. In all instances, patients have been under the observation of dermatologists for months or years. In addition, positive pathologic evidence of the disease has been recorded in each while under our observation. There were 130 men and 70 women; 27 patients were under 40 years of age, 91 were between the ages of 40 and 60, and 82 patients were over 60 years. The youngest patient treated was 17; the oldest patient 84; both were males. On initial examination about 40% of the patients were in the erythema

TABLE 2

GEOGRAPHIC DISTRIBUTION

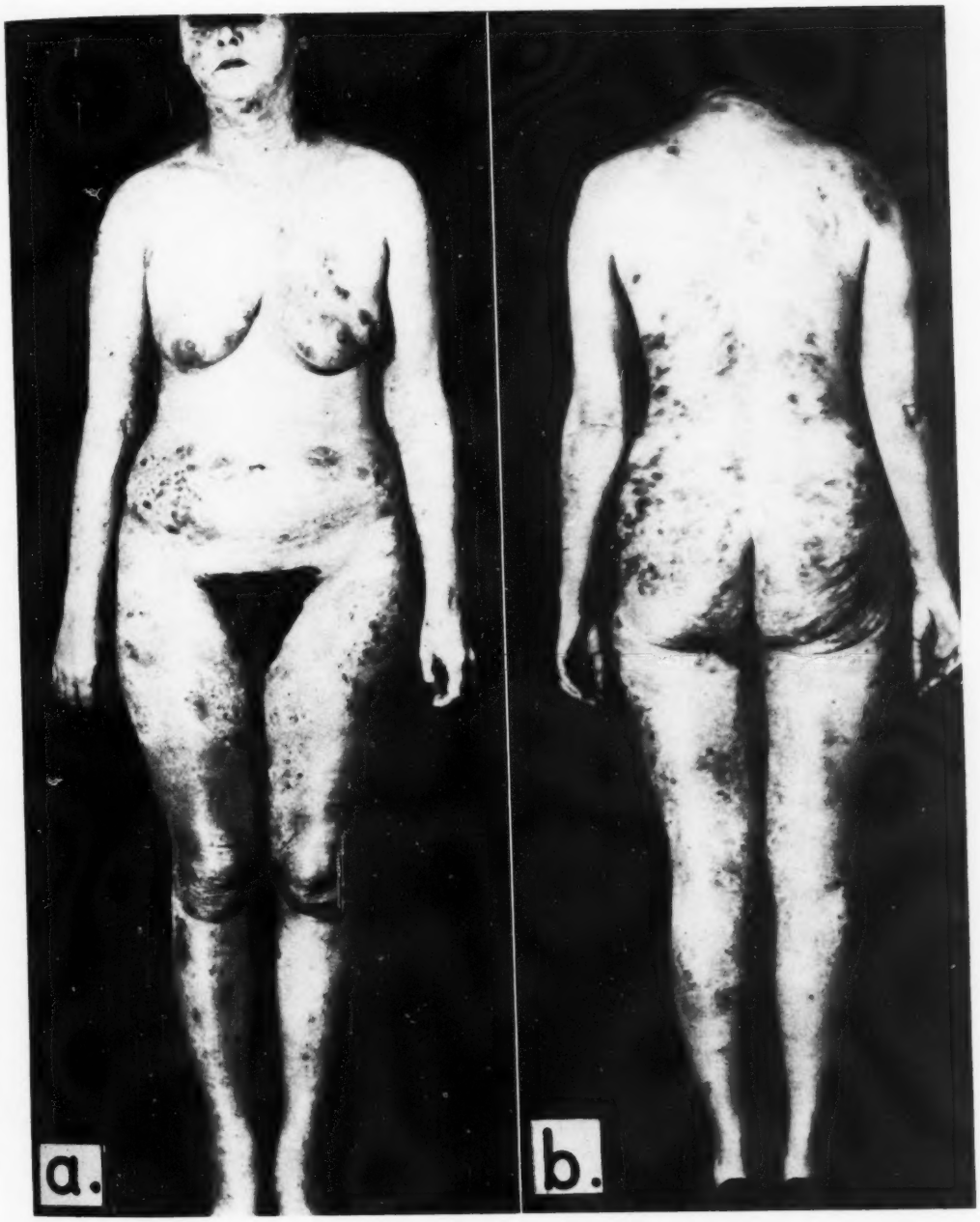
Location	*Number of Cases*
U.S.A.	
Eastern	148
Midwestern	28
Western	14
Foreign	10
Total	200

and plaque stage. Another 40% were in the tumor stage; approximately 10% were in the ulcerative stage, in extremis, and about 10% were in the early erythematous stage and had never been subjected to any form of treatment. All patients had a general medical examination, a dermatologic survey and blood studies by a hematologist. The patient usually brought a prepared slide and this was reviewed by our pathologists. If the interpretation of the slide was equivocal, further biopsy specimens were obtained before treatment. The recorded material was then reviewed by the radiologist who, with the physicists, was responsible for the actual electron beam therapy. The chief contraindication to electron beam therapy was a greatly depressed hemogram resulting from the recent administration of cytotoxic agents.

Results of Treatment

In evaluating the treatment results with the electron beam in mycosis fungoides it should be remembered that most of the patients in this series had been given the benefit of every conceivable treatment measure, including radiotherapy and chemotherapy before they came to the Lahey Clinic. Because of the rarity and seriousness of this disorder, the natural drift of patients is to the large treatment center and in all cases the disease had been very well managed. In many instances our contact with the patient was in the nature of a "last resort" experience. It soon became evident that almost without exception, the initial response to electron beam therapy was dramatic. Figure 3, A and B shows a patient with the infiltrative plaque and nodular stage of mycosis fungoides. A classical background of persistent "eczema" was obtained. The pathologist's diagnosis was mycosis fungoides. The response to an initial course of electrons is shown in figure 3, C

FIG. 3, A and B

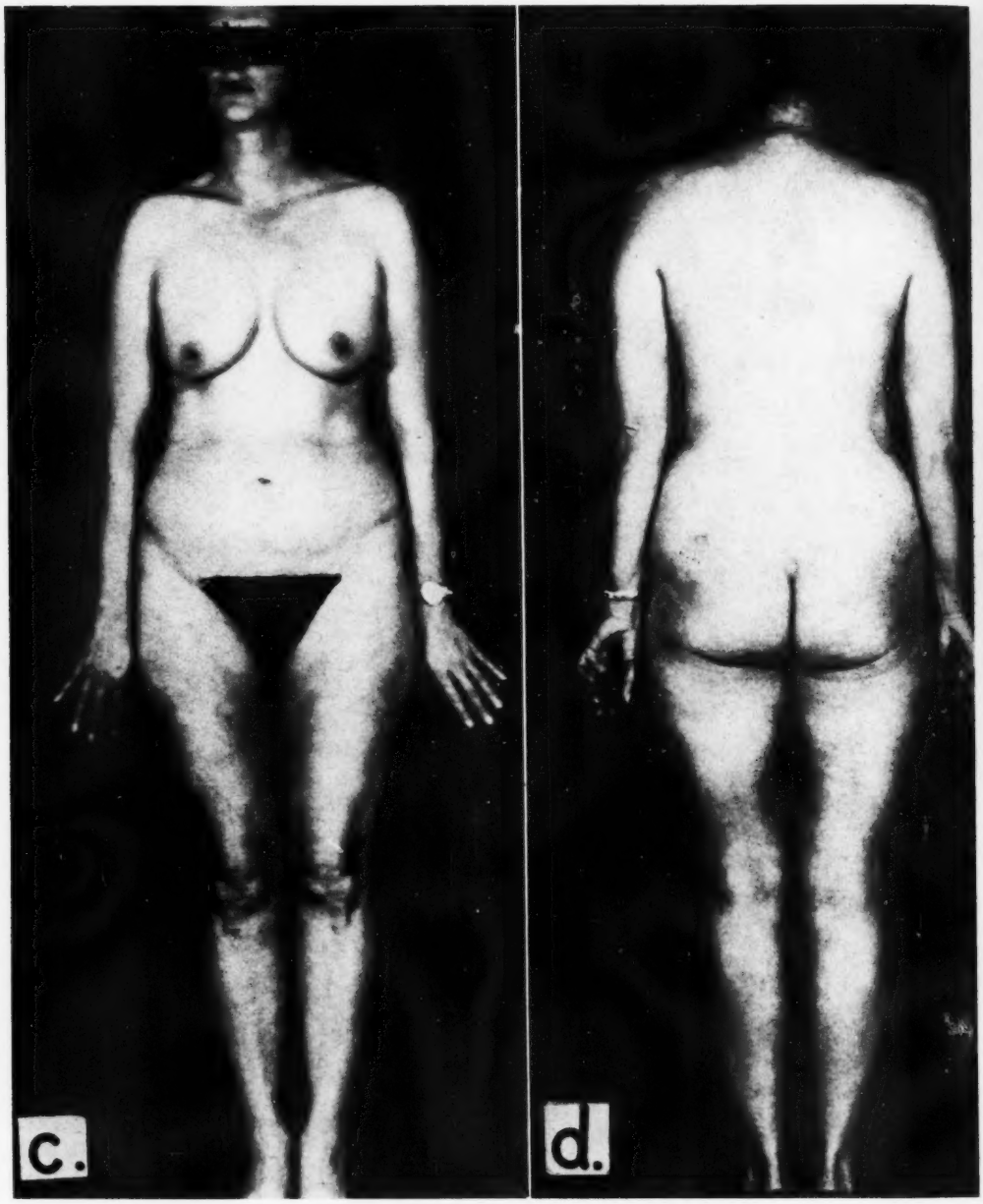


Plaque stage of mycosis fungoides before electron beam therapy.

and D. This patient fortunately has had a long remission following a single course of electron therapy.

The male patient demonstrates the type of extensive lesions seen in many of the patients in this series (Fig. 4). In spite of previous

FIG. 3, C and D



Plaque stage of mycosis fungoides after electron beam therapy.

radiotherapy, the response in three weeks was striking. About 90% of the nodules and tumors had subsided—not only those on the head and shoulders but also those on the entire cutaneous surface which was similarly involved. Unfortunately, a severe pulmonary infection developed in this case; a fulminating toxic process was followed by a flare-up of

FIG. 4

(A) Patient with extensive lesions of mycosis fungoides before electron therapy. (B) Response three weeks after electron therapy. (From Wright et al., Radiology, October 1956.)

the lymphoma and the patient died of generalized, reticulum cell lymphomatous disease.

Since all therapy for lymphoma cutis, including electron beam, is palliative only recurrences are to be expected (Table 3). Most patients require retreatment with some form of ionizing radiation in 3 to 6 months. Scattered infiltrative lesions may be treated by the referring dermatologist or radiologist with conventional x-ray therapy. If the recurrence is characterized by widespread dissemination of lesions, another course of total body radiation with electrons is indicated. For heavily infiltrated plaques and tumors, electrons are ineffectual because of failure to penetrate. In our experience, 2 Mev. x-ray radiation is effective in a dose range of 400 r for small lesions or up to 1200 r in fractional doses.

TABLE 3

LONGEVITY AS OF AUGUST 31, 1960
200 Patients

Interval Since Electron Treatment	*Female*	*Male*
1 to 4 years	36	44
5 to 9 years	8	16
Total	44	60

Although the natural course of the disease has been recorded for over a century, the ability of the host to survive in spite of the disease varies greatly. Patients with minimal infiltrative lesions have been observed who survived only 6 months. Other patients with what appeared to be advanced reticulum cell lymphoma have responded surprisingly well and have survived long enough to die of other causes.

It soon became evident from the response in individual patients that some patients might outlive their skin tolerance to electrons. For this reason patients were given adjunct therapy. Corticosteroids and antimalarials were found to be effective in the inflammatory eczema-psoriasis stage before the lesions became infiltrated. Patients with more advanced disease and especially those with poor response to repeated therapy with the electron beam were given cytotoxic agents. Of these, chlorambucil, in doses of 2 to 6 mg. daily for short courses, was found to be the safest and most effective agent.[3] Experience with this combined electron beam and chemotherapy suggests that the usual interval between courses of electron beam therapy may be prolonged. Some patients requiring a 3 month retreatment schedule could safely return in 4 months or longer in some instances. By combinations of these technics the life expectancy of most patients has been extended measurably beyond the usual 2 year survival period. The longest survival in the nodular and plaque stage has been 7 years.

Discussion

Following treatment with the electron beam of our first patient suffering from lymphoma cutis,[1] interest in the use of this modality has increased. Generators producing electrons have been established on both coasts. The biologic properties of electrons on bacteria

and viruses, spores and molds have previously been studied. Many interesting experiments on the effects of electrons on a variety of substances, both organic and inorganic, are in progress. The physical aspects of megavolt electron therapy were presented by Wright and associates.[4] Improvement in the original apparatus and comments on the dangers and the precautions taken to avoid overexposure in electron beam therapy were recorded. Modifications of the original two story generator now in use were presented.

The successful use of the electron beam in a number of dermatologic conditions other than lymphoma attests to the further usefulness of this modality.[5] In a recent paper, Johnston and his group[6] discuss the successful use of the electron beam in lymphoma cutis, Kaposi's hemorrhagic sarcoma, metastatic implants from carcinoma of the breast and localized basal and squamous cell carcinoma.

Whole body superficial irradiation with beta rays generated by strontium-90 was reported by Horwitz and others[7] in England. Regression of lesions of mycosis fungoides in 3 patients with widely disseminated disease was presented. As various investigators study this problem, this experience will result in improved technics, dosage schedules, intervals for optimum treatment and adjunct therapy in cases of lymphoma cutis.

Summary

Experience with the management of 200 patients with mycosis fungoides treated principally with total body irradiation by high energy electrons indicates that this is the most effective treatment available today. In most cases some type of adjunct chemotherapy is necessary. Our impression is that some desperately ill patients with mycosis fungoides may be salvaged for many months beyond the usual course of the disease. Patients treated in the early, generalized, infiltrative stage have a better prognosis than those treated in later stages.

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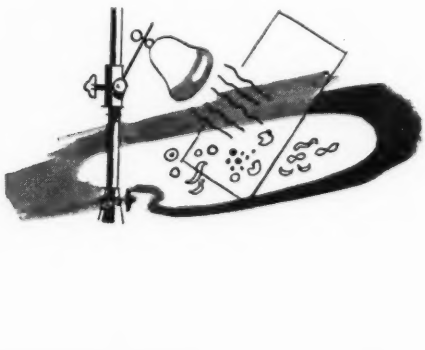


Arthrodesis of the Hip:

Indications for and End Results of Such Operations*

EARNEST B. CARPENTER, M.D., and
JAMES W. BANKS, M.D.,† *Richmond, Va.*

Though reconstructive operations on the hip are finding favor, the authors believe that arthrodesis has a definite place in the management of certain disabilities especially in the younger age group.

IN THE PAST DECADE, great emphasis has been placed on the wide variety of reconstructive procedures of the hip. Many such procedures have great merit and enable the orthopedist to preserve motion of the hip and at the same time relieve the patient of disabling pain. Unfortunately, the end results of many such reconstructive procedures have left the patient with a painful disability requiring further definitive surgery. Arthrodesis of the hip has received little emphasis in the past decade, but it remains as a sound orthopedic procedure with a high incidence of success. Admittedly, the long period of immobilization following operation for hip fusion is a justifiable reason for objections to this operation.

With no attempt to compare the advantages or disadvantages for reconstructive procedures of the hip versus arthrodesis of this joint, we wish to present an end result study of 18 cases of arthrodesis of the hip. These patients were all treated at McGuire Veterans Administration Hospital, Richmond, and covered the years 1949 through 1959. During the same period of time at the same hospital, 26 patients underwent reconstructions. It is immediately apparent that in this institution at least, arthrodesis of the hip in the past 10 years was a less popular procedure than reconstructive procedures. Again, we wish to emphasize that no attempt is made to compare the end results of these two groups of cases. The pathologic processes for which arthrodesis of the hip was carried out are summarized in table 1.

The patients were all male, the youngest being 24, the oldest being 58 years of age, with the average age at time of operation being 43.9 years. Twelve of the patients were Caucasian and 6 were Negro.

TABLE 1

Septic arthritis, old	1
Fracture femoral head with nonunion	3
Fracture femoral neck with aseptic necrosis	4
Femoral prosthesis with intractable pain	1
Fracture dislocation of hip with traumatic arthritis	2
Traumatic arthritis, cause undetermined	1
Tuberculosis of hip	1
Old Perthe's disease with traumatic arthritis	1
Gunshot wound, old, with traumatic arthritis	2
Bone cyst, femoral head	1
Hypertrophic arthritis	1
Total	18

The type of operative procedures employed are summarized in table 2.

The average period of immobilization following operation was 4.2 months, with the exception of the 2 procedures in which Schneider nails were used. The initial immobilization was a double spica cast which in almost every instance was maintained for 3 months after operation, following which either a single spica or a one and one-half spica was applied. In 2 cases in which the Schneider nail was used, a single spica cast was used for 2 months following operation, after which full weight-bearing was resumed. The longest period of immobilization was 9 months, this being in the case of tuberculosis of the hip.

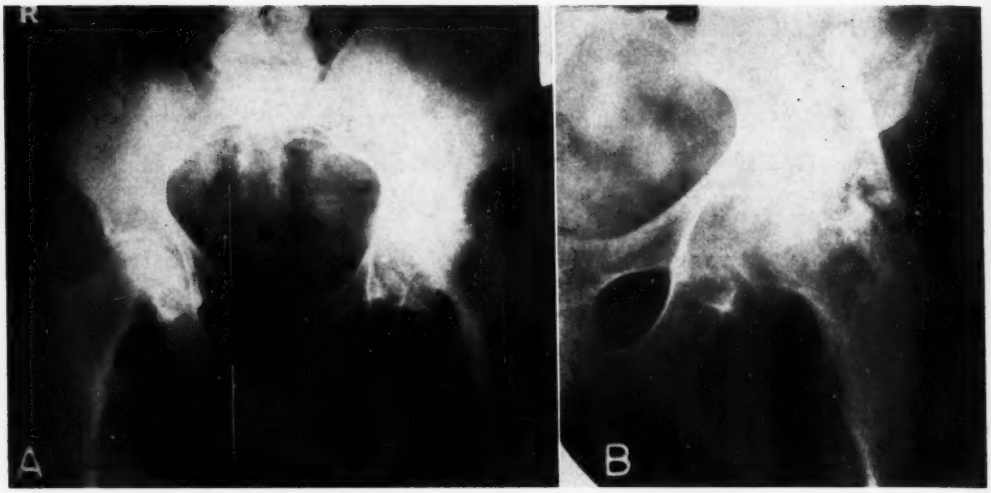
TABLE 2

Ghormley	9
Chandler	6
Brittain	1
Schneider	2
Other	1
Total	19

*Read at the Thirty-Second Annual Clinical Session of Virginia State Orthopaedic Society, Richmond, Va., April 9 and 10, 1960.

†From the Department of Orthopaedic Surgery, McGuire Veterans Administration Hospital and the Medical College of Virginia Hospital, Richmond, Va.

FIG. 1

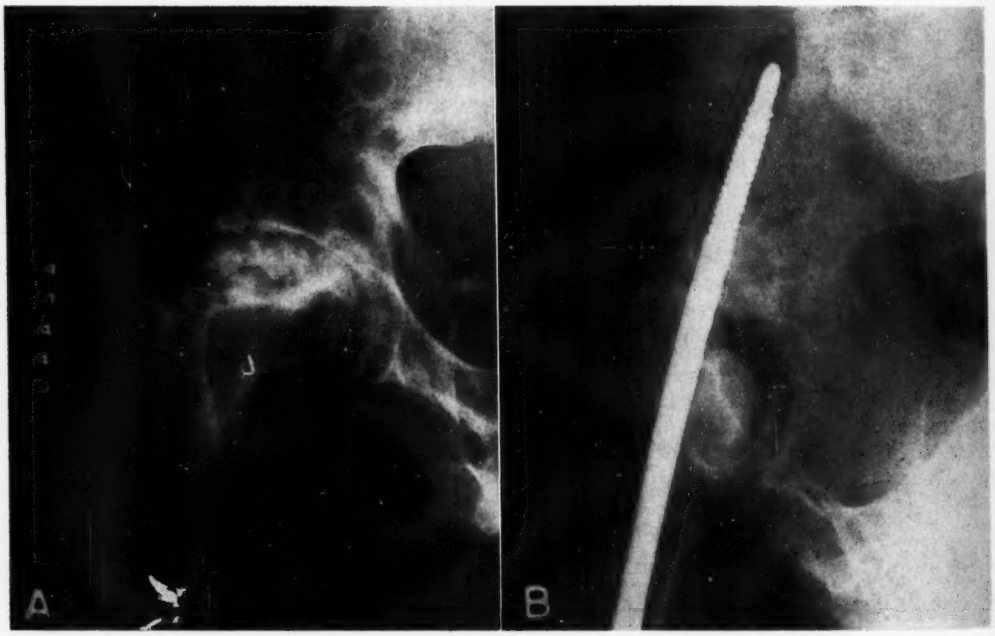


(Case 3) (A) Preoperative. (B) Six years after operation.

Results

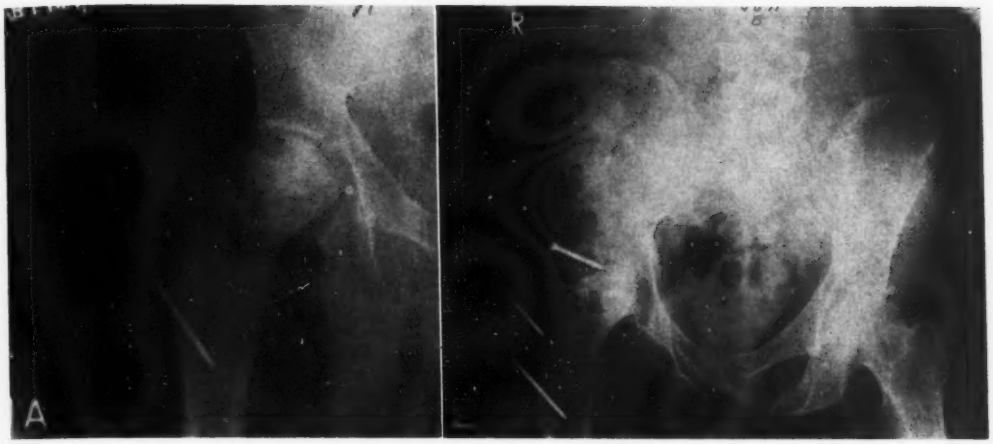
Nineteen operative procedures were carried out in the 18 cases. In one case of traumatic arthritis a Chandler operation had been performed initially which resulted in failure of fusion. This was followed by a Brittain fusion which was successful. Among the 18 cases there were 2 failures of fusion, but in both of these instances the patients were free of pain and stated they were improved over their preoper-

FIG. 2



(Case 5) (A) Marked degenerative arthritis. (B) One year after operation with Schneider nail in place.

FIG. 3

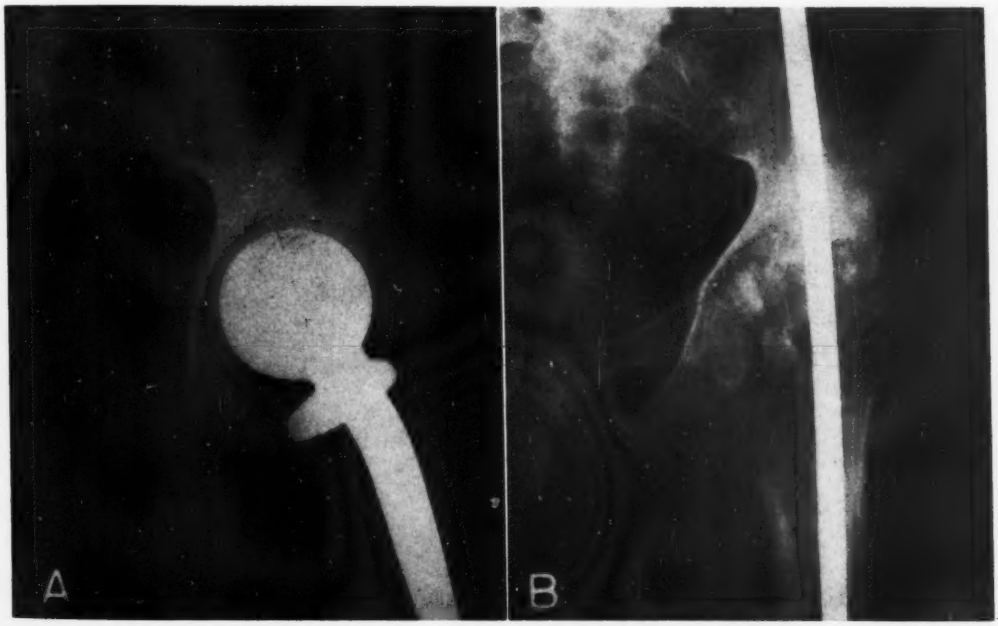


(Case 6) (A) Aseptic necrosis of head. (B) Firm bony union 3 years after hip fusion.

ative condition. In only one case was a subtrochanteric osteotomy performed in association with the fusion. The group was followed for an average of 2 years, the longest follow-up being 5 years, the shortest being 9 months.

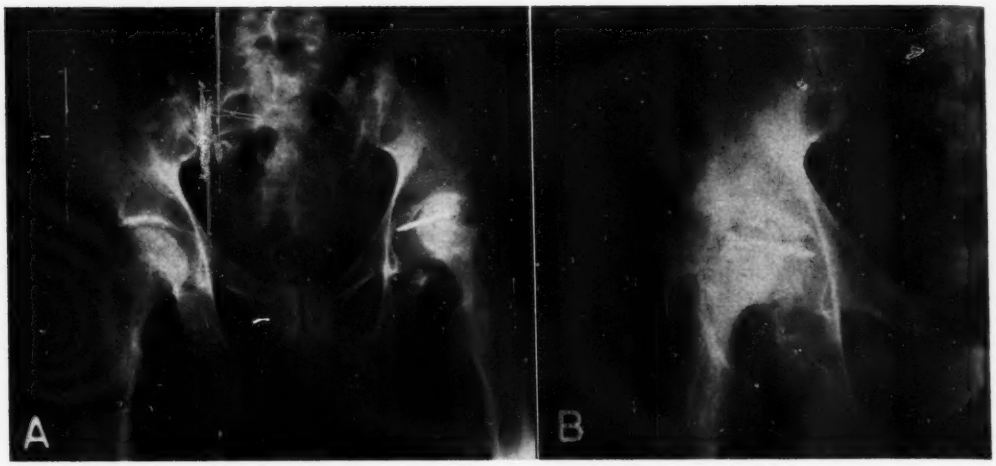
To further our information about these patients, questionnaires were sent to 14 of the patients included in the study group, and the 4 remaining patients were examined personally by us. One patient, who had a complete loss of the head and neck of the right femur due to wounds from shell fragments plus multiple other wounds of the same extremity, drained intermittently following his fusion. Clinically

FIG. 4



(Case 10) (A) Thompson type prosthesis before operation. (B) Bony union with Schneider nail in place one year following operation.

FIG. 5



(Case 11) (A) Traumatic arthritis with metallic screw in posterior aspect of acetabulum. (B) Firm bony union shown 18 months following operation.

and by x-ray the patient did not have a solid fusion, however, he was bearing weight on his hip and was free of pain. Subsequently because of recurrence of his infection from the multiple wounds, the right leg was amputated at the high thigh level at another institution. Another patient, having a Chandler hip fusion with failure of complete fusion, is at the present time in another Virginia hospital in a terminal state because of fibrosarcoma of the neck with widespread metastasis. It is reported at that hospital, however, that he has had a solid fusion in the period of 1955 to the present, during which time he has been under treatment for the fibrosarcoma. He has had no complaints referable to his hip and exhibits a solid fusion, both by x-ray and by examination. A summary of the questionnaires is tabulated in table 3.

Postoperative drainage occurred in 2 instances, one in the previously mentioned patient with wounds of the hip due to shell fragments; the other drainage occurred in a patient with a nonunion of a fracture of the femoral neck and who had a severe infection of the hip on admission. The hip fusion was carried out after the infection had been controlled; following operation drainage recurred intermittently for 3 months. Complete fusion in this patient is questionable, though he is free of pain and able to bear full weight. A summary of all cases is tabulated in table 4.

TABLE 3

	Yes	*No*
Full weight-bearing	12	6 (use cane)
Sits down comfortably	15	3
Puts on shoe and sock without aid	15	3
Able to work	14	4
Hip-pain	Some 14	None 4
Knee-pain	Some 5	Several 13
Does feel that operation helped	17	1

Discussion

In reviewing the literature, the first mention of arthrodesis of the hip was found in 1908, when Albee[1] reported a case of intra-articular fusion performed in a 59 year old policeman. Stinchfield and Cavallaro[2] reported 117 cases of arthrodesis of the hip performed between 1935 and 1946 at New York Orthopaedic Dispensary and Hospital. In their study, failure of union occurred in 23% but they emphasized that 8 of the patients with failure of fusion were not incapacitated by the lack of fusion. Apley and Denham[3] reported a series of 55 cases of arthrodesis in which the operation was done without osteotomy in 33 and with osteotomy in 23. In their series failure of fusion occurred in 20 patients in whom no osteotomy was performed and in only one instance was failure of fusion found among the operations with osteotomy. Their findings are further substantiated by Thompson[4] who believes that osteotomy with fusion is the procedure of choice. He thinks osteotomy removes motion

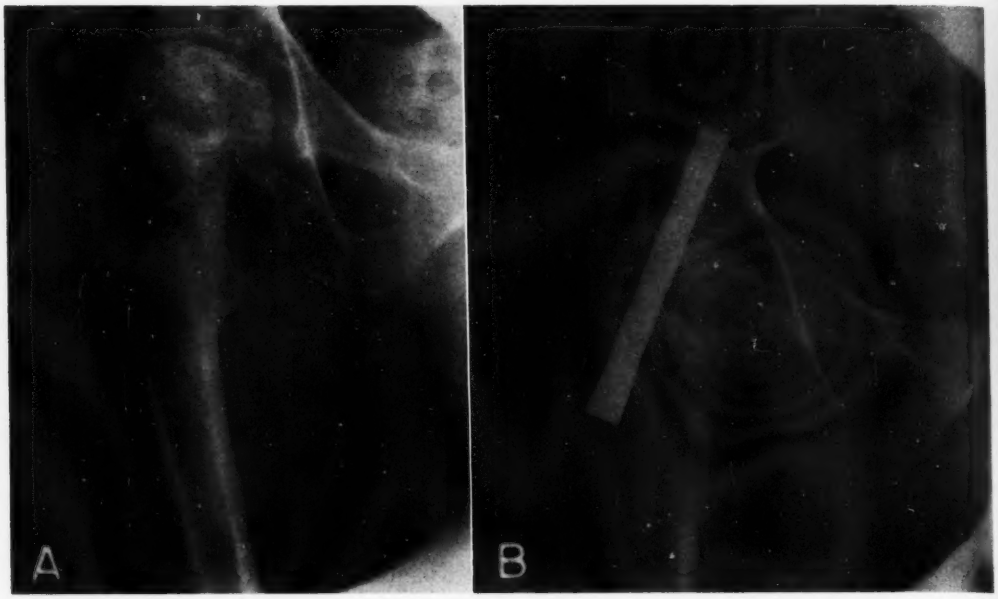
TABLE 4

Case	*Age*	*Reason for Fusion*	*Type of Fusion*	*Time in Cast*	*Complications*
1	49	Osteoarthritis	Ghormley	4 mos.	None
2	31	Aseptic necrosis	Ghormley	6 mos.	None
3	57	Aseptic necrosis	Chandler	6 mos.	None (Fig. 1, A and B)
4	24	Gunshot with loss of head and neck	Chandler	3 mos.	Postoperative drainage for 2 mos.
5	32	Aseptic necrosis	Ghormley	5 mos.	None (Fig. 2, A and B)
6	53	Degenerative arthritis	Schneider	5 mos.	None (Fig. 3, A and B)
7	35	Aseptic necrosis	Ghormley	6 mos.	None
8	38	Traumatic arthritis	Ghormley	6 mos.	None
9	47	Neck fracture with postoperative infection	Chandler	6 mos.	Postoperative infection with drainage for 3 mos. (fibrous union)
10	25	Painful prosthesis	Schneider	2 mos.	None (Fig. 4, A and B)
11	31	Traumatic arthritis	Ghormley	6 mos.	None (Fig. 5, A and B)
12	56	Gunshot with traumatic arthritis	Chandler	6 mos.	Nonunion, re-operated
		Re-operated	Brittain	3 mos.	None
13	53	Tuberculous arthritis	Ghormley	9 mos.	None
14	29	Bone cyst femoral neck	Ghormley	6 mos.	None (Fig. 6, A and B)
15	34	Aseptic necrosis	Chandler	6 mos.	None (Fig. 7, A and B)
16	37	Gunshot with loss of head and neck	Whitman with bone graft	5 mos.	None (Fig. 8, A and B)
17	38	Traumatic arthritis	Ghormley	6 mos.	None (Fig. 9, A and B)
18	58	Aseptic arthritis	Ghormley	6 mos.	None (Fig. 10, A and B)

FIG. 6

(Case 14) (A) Degenerative arthritis of hip with benign bone cyst in lateral aspect of femoral head and neck. (B) Firm bony fusion of hip one year after operation.

FIG. 7



(Case 16) (A) Early aseptic necrosis of head secondary to old intracapsular fracture of femoral neck. (B) Firm bony union 9 months after operation.

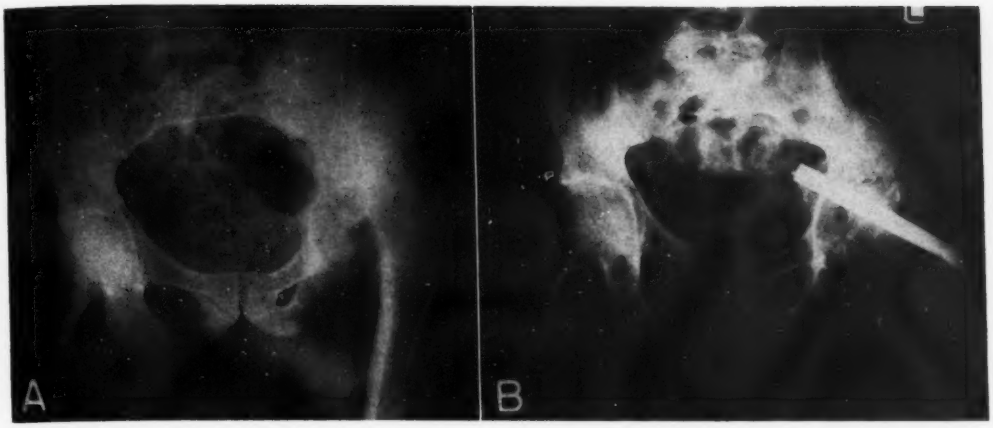
from the hip joints and permits early bony union of the hip to occur before healing of the osteotomy is sufficient to produce the motion of the hip joint.

It is the general consensus in all of the articles reviewed that the greatest disability following procedures for fusion of the hip was stiffness of the knee as a result of the long period of immobilization. It is thought by some that immobilization could be satisfactorily maintained and knee motion regained by a bivalve cast posterior and just above the knee joint and by giving the patient knee motion exercises after the initial 6 weeks of immobilization.

FIG. 8

(Case 17) (A) Complete loss of head and neck and proximal portion of femur secondary to gunshot wound and infection. (B) Shaft of femur shown fused to the old acetabulum with good bony union.

FIG. 9



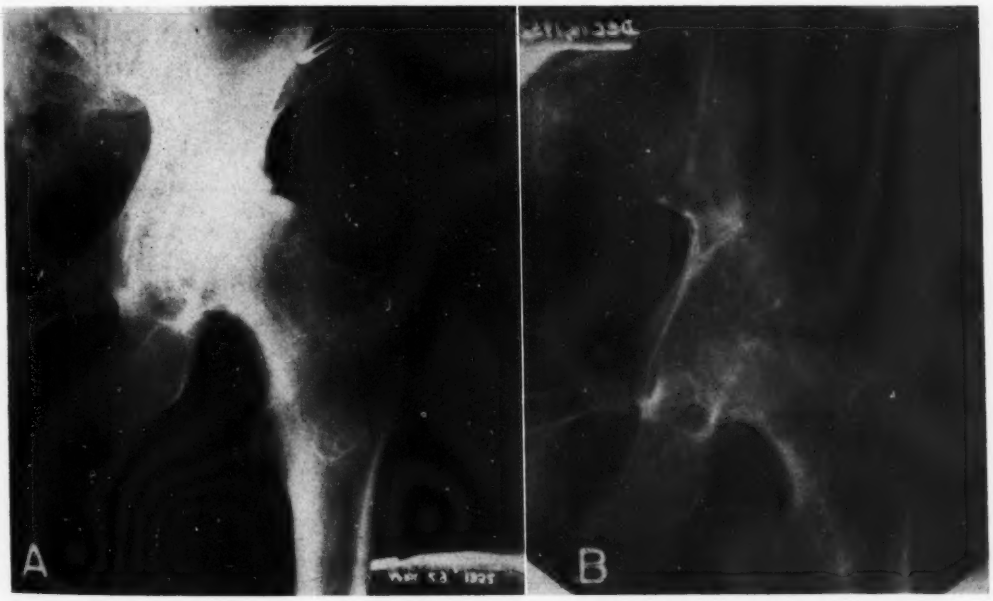
(Case 18) (A) Posterior dislocation of left hip of 2 months duration. (B) Firm bony fusion one year after operation.

Apley and Denham[3] have found good results by the use of traction with a Kirschner wire through the distal femur and holding the patient on a divided bed. Knee exercises were started on the second postoperative day and, after 6 weeks, the patient was placed in a weight-bearing short spica cast for 6 weeks, following which all immobilization was discontinued. This procedure was carried out only in those cases in which osteotomy had been performed in addition to the arthrodesis.

Conclusion

A summary of 18 cases of arthrodesis of the hip is presented. Nineteen operative procedures were carried out in this series with solid fusion as shown by clinical and x-ray examination being obtained in 17 instances for a per-

FIG. 10



(Case 15) (A) Destructive changes secondary to old infection. (B) Solid union present 5 years after fusion.

centage of failure of fusion of 11 per cent. The 2 instances of failure of fusion were improved over their preoperative condition. It is believed that fusion of the hip is preferred to reconstructive procedures upon the hip joint, and is the operation of choice in the young or relatively young individual whose occupation requires long periods of standing or walking.

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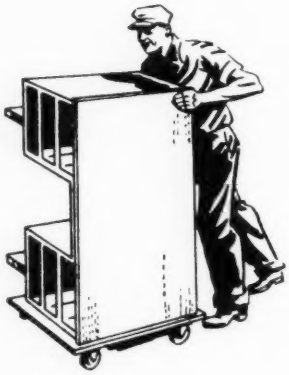

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Surgical Management of Anorectal Complications of Chronic Ulcerative Colitis*

PAUL J. FUZY, JR., M.D.,† *Fort Lauderdale, Fla.*

Several complications of ulcerative colitis may show themselves during the course of disease. They must be recognized and be thoroughly considered from the standpoint of surgical management.

VARIOUS ANORECTAL COMPLICATIONS occur in approximately 20 to 25% of patients afflicted with chronic ulcerative colitis. They do not threaten the patient's life, but add greatly to his discomfort and disability. Therefore, it is important that we know how to treat these conditions. It is, however, even more important that we know how *not* to treat them, since an improperly managed anorectal complication may necessitate ileostomy in a patient who might otherwise have been managed medically.

The complications encountered will be discussed in order of their frequency, with the exclusion of carcinoma and polyposis. Although these are recognized complications of ulcerative colitis occurring in the anorectal area, it is thought that their management is beyond the scope of this presentation.

Stricture

Stricture formation may occur anywhere in the colon as a result of ulcerative colitis. It is, however, most common in the rectum and may be either tubular or annular. Annular stricture may respond sufficiently to mechanical dilatation to relieve symptoms. Low annular stricture may be treated during quiescence of the colitis by posterior proctotomy with suture of a flap of mucosa over the wound to insure against reapposition of the cut surfaces.

For tubular rectal stricture, Abel[1] has described hydraulic dilatation by means of a balloon attached over the end of a No. 10 catheter. This is inserted into the rectum and water is injected daily in slowly increasing amounts. By this method he has been able to increase the capacity of the rectum from one-half ounce to from 5 to 11 ounces in an average time of 14 months. By combining this treatment with antiseptic irrigations, he has been able to accomplish this even in the face of active inflammation.

In a rare case stricture may be so severe or so extensive that ileostomy will be required. (Throughout this presentation the term "ileostomy" will be used to indicate radical surgical attack upon the ulcerative colitis. No attempt will be made to choose between ileostomy alone, ileostomy with concomitant colectomy, or ileorectal anastomosis.)

Abscess and Fistula

Probably the most painful and disabling of the anorectal complications are perianal and perirectal abscesses and their resultant fistulas. It is interesting that Crohn[2] has found a high incidence (23.5%) of abscesses with rectal, rectovaginal and recto-urethral fistulas even in segmental ulcerative colitis in which the rectum and rectosigmoid were not involved. During activity of the colitis treatment of these conditions must be conservative. Surgery is limited to opening of the abscess cavity to provide drainage and relief of pain. Following drainage, antibiotics should be used systemically because the very low resistance of these patients may allow spread of infection to continue even after release of the pus.

When the colitis is quiescent, it is possible

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in selected cases to perform fistulotomy or fistulectomy. Careful selection of cases is necessary, however, since it is always possible that the stress of operation may result in an exacerbation of the colitis. Should this occur, wound infection will follow and a breakdown of tissue with destruction of the sphincter, stenosis and incontinence. In such cases ileostomy will be necessary.

Because of this ever-present risk, it is believed that definitive surgery for a fistula should be reserved for those in whom distressing symptoms of discharge and pain are present, and in whom the ulcerative colitis has been quiescent for some months. The exact length of quiescence to permit a reasonably safe operation must be determined for each individual by taking into account previous history of exacerbations and remissions.

Hemorrhoids

Either thrombotic external or prolapsed internal hemorrhoids may occur during ulcerative colitis. For thrombosed ones conservative measures will usually suffice. These include hot compresses or sitz baths, witch-hazel compresses, and orally administered proteolytic enzymes or streptokinase-streptodornase combination. If these measures are not adequate to reduce swelling and pain, enucleation of the clot may be necessary. This is to be avoided if possible, however, because of the tendency of the wound to become infected and indolent with the result that postoperative discomfort may equal that which the procedure was done to alleviate.

Prolapsed hemorrhoids are also to be treated by the conservative method outlined above. Hemorrhoidectomy done during the active phase of ulcerative colitis will almost surely be followed by breakdown of the wound and fistula formation with possible incontinence. Rectovaginal fistula is a frequent result of such ill-advised operations. For this reason it is well to reiterate the familiar warning that every patient should have a thorough sigmoidoscopy prior to any anorectal operative procedure. This will prevent a hemorrhoidectomy being done to control bleeding in a patient who is actually bleeding from an unrecognized ulcerative colitis.

During remissions of the colitis it is possible to carry out more definitive treatment in patients whose symptoms have been severe. Treatment by sclerosing injection may be adequate for small hemorrhoids which are entirely or predominantly internal. Large mixed hemorrhoids may require hemorrhoidectomy. Here the severity of symptoms must be weighed against the possibility of "lighting up" the colitis before decision about an operation can be made. If there is any doubt in the surgeon's mind, conservative therapy is recommended.

Anal Fissure

It must be stressed at the outset that the fissure seen as a complication of ulcerative colitis is basically different from the usual type. The fissure under discussion here is the result of infection and bears no relationship to configuration of the sphincter. Its behavior may be better understood by thinking of it as a partially unroofed intracutaneous abscess with inadequate drainage. When the colitis becomes quiescent and diarrhea ceases, the fissures, which are often multiple, will heal spontaneously. For this reason it is usually only necessary to control pain by local measures. These include the use of topical anesthetics in ointment or oil solution, and cortisone-containing suppositories. The patient should be instructed to hold the suppository in the anal canal for 15 to 30 seconds before inserting it into the rectum. In this way some of the medication is deposited immediately on the involved area. Some relief also may be obtained from the use of heat in the form of sitz baths, compresses, or rectal irrigations.

If these palliative measures fail, limited surgical treatment is indicated. In this type of fissure it is necessary only to provide adequate drainage. Excision of the fissure is not necessary (and, of course, could not be done in the face of active colitis). Under local or regional anesthesia the fissure wound is extended well past the anal verge so it may heal from the anal canal outward. Recurrence after such an operation is rare because of the basic nature of this type of fissure as was described above, i.e., there is no mechanical factor in its etiology.

Incontinence

Some degree of incontinence is seen as a result of general debility and weakness in many advanced cases of ulcerative colitis. This, of course, does not require any more specific treatment than management of the colitis.

Severe incontinence may occur from fibrosis of the sphincter or its destruction as a result of spontaneous abscesses, or instances resulting from unwarranted anorectal surgery done for one of the above complications. When such irreversible changes have occurred, ileostomy will be the only remedy.

Summary

The anorectal complications of chronic ulcerative colitis are, (1) stricture, (2) abscess and fistula, (3) hemorrhoids, (4) anal fissure, and (5) incontinence. Carcinoma and polyposis constitute 2 more serious anorectal complications, but discussion of their management was thought to be outside the scope of this presentation. Treatment of anorectal complications while the underlying disease is active is limited to palliative measures, since a radical surgical attack is almost certain to be followed by sloughing of tissue and destruction of the sphincter.

Even during remissions, corrective anorectal surgery must be done with care, in selected patients in whom pain and disability of the complications are severe enough to justify the risk of initiating an exacerbation of the colitis. Caution and conservatism must be our watchwords.

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Discussion (Abstract)

Dr. Matthew A. Larkin, Miami, Fla. Dr. Fuzy has presented another of the distressing complications of ulcerative colitis well. I have no real experience in the mechanical treatment of tubular or circular strictures in this disease, save the use of passing small to larger caliber sigmoidoscopes to assay the progress of pathologic changes. I am tempted to view an individual with tubular stricturing as a candidate for colectomy, since this complication rarely occurs in anything but severe cases.

Perianal and perirectal abscesses should always be drained surgically, but this must be done with a minimum amount of surgical incision and tissue destruction. The so-called treatment of "laying wide open" an abscess will only leave a large infected secondary wound in many cases of ulcerative colitis.

In chronic low grade ulcerative colitis all fistula-in-ano need not be a part of the disease and the judicial use of surgical judgment must be made. I recently saw a patient with chronic cord fistula of 6 years duration who had been denied operation because he had ulcerative colitis. The truth is that his condition had been quiescent for almost 3 years, with only an occasional episode of mild diarrhea of 3 to 5 stools daily. He responded normally to simple fistulotomy. The inherent danger of mitotic activity in fistulas after 5 years has been repeatedly pointed out by Rosser and has been observed in our own experience.

It seems elementary for Dr. Fuzy to point out that adequate sigmoidoscopic examination precede hemorrhoidectomy, but in the past year I have made the diagnosis of ulcerative colitis twice on patients who had undergone anorectal surgery elsewhere and were referred to me. One, an 18 year old student, had anal wounds which remained infected and open 4 months postoperatively after a fissurectomy; the other, a 42 year old executive, continued to pass bloody mucus 3 months after hemorrhoidectomy.

I have enjoyed Dr. Fuzy's conservative and complete coverage of this subject, and I am grateful for the opportunity to make these few comments.

A Controlled Short-Term Evaluation of a New Antihypertensive-Diuretic Agent, Benzydroflumethiazide

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This variant of the "thiazide" group acts in a similar manner as the others, pharmacologically and clinically. Side-effects will show up sooner or later, as with the others. The authors also demonstrate that, as with all antihypertensive agents, there are failures on medication and that the evaluation of antihypertensive effect is extremely difficult because of the great number of variables involved.

BENZYDROFLUMETHIAZIDE (Naturetin)* is the 3-benzyl derivative of hydroflumethiazide. As a diuretic agent it is reported to be 100 times more potent, milligram for milligram, than chlorothiazide. Like its diuretic thiazide antecedents, it also possesses significant antihypertensive properties. The purpose of this study was to assess its effectiveness in lowering blood pressures in patients with essential hypertension.

Material and Method

For this single-blind study, 41 patients attending the hypertension clinic at the Mercy Hospital were selected. Of these, 14 failed to attend regularly and were discarded from the study. Of the 27 patients remaining, 4 had control diastolic pressures between 130 and 139 mm. Hg., 4 had control diastolic pressures between 120 and 129, 8 between 110 and 119, and 11 between 100 and 109. Sufficient screening tests were performed so all patients could reasonably be labeled "essential" hypertensives. Of the patients included in the study, 8 were white (4 male and 4 female) and 19 were colored (2 male and 17 female).

All patients were initially placed on dummy tablets identical with 5 mg. tablets of the active material; one tablet was given twice daily until a stable baseline was obtained and for a minimum of 2 weeks (i.e., for a minimum of 3 readings at weekly intervals).** The active substance was then substituted in a dose of 5 mg. twice daily. If no appreciable effect on the blood pressure was noted at the end of 3 weeks, the dose was increased to 10 mg. twice daily. Dosage was again increased by 10 mg. daily at 2 to 3 week intervals up to a maximum of 20 mg. twice daily. If no significant fall of blood pressure was observed after 2 to 3 weeks on 40 mg. daily, i.e., after a total period of 8 to 12 weeks on the active drug, a failure was accepted and the patient was changed to another form of therapy. If significant depression of the blood pressure occurred, the patient was maintained on the drug for a minimum of 8 weeks. In all but 3 patients, in whom a significant fall in blood pressure was observed, a second period on identical dummy tablets was instituted at the same dosage level (2, 4, 6 or 8 tablets daily) that had been reached on the active drug. The dummy was continued until a definite upward trend in the blood pressure was established, not necessarily until the pressures returned to their former levels. It was not believed justified to allow the more severe hypertensives to regain their previous levels of diastolic pressure.

The second period on dummy tablets was instituted for several reasons: (1) to re-

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*Supplies of the drug (Naturetin, Squibb) and of identical dummy tablets were graciously provided for this study by Dr. R. C. Merrill of The Squibb Institute for Medical Research.

**Except for one patient, Case 2, whose clinical status made it most desirable to begin therapy promptly; therefore only 2 readings, one week apart, were obtained as a baseline.

confirm in reverse the efficacy of the active drug; (2) to exclude the possibility that the fall in pressure was coincidental and would have occurred at that time independent of the drug; (3) to exclude the possibility that the fall in blood pressure was related to psychic factors such as increasing confidence on the part of the patient, improving rapport with the staff, etc.; (4) to gain some knowledge of the duration of action of the drug; and (5) to provide a further period of correlation between weight and level of blood pressure.

All patients were seen at weekly intervals, with rare exceptions for specific reasons. During the second period on dummy medication, especially when pressures were slow to rise, visits were sometimes spaced at two or three week intervals. At each visit every patient was weighed on balance scales. Because blood pressure determinations are subject to so many variables, including variation between observers, especially if the same meticulous technic is not scrupulously observed, we made every effort to reduce such variables to a minimum. Patients were seated quietly for a minimum of 15 minutes before readings were obtained. At each visit 4 readings were made with a mercury manometer at intervals of a few minutes and the mean of these 4 readings was recorded as the day's pressure. The point of maximum change was taken as the diastolic reading; when this was not recognizable, the point of disappearance of sound was recorded. Especial attention was paid to details that are important for accurate and comparable records: the patient's same arm was used for all readings at all visits, cuffs were applied snugly, and the mercury column was allowed to fall past systolic and diastolic endpoints at a maximum rate of 2 mm. per heart beat. We personally made at least 75% of all the readings in the entire study, and frequently cross-checked each other's readings; the balance of readings were made by competent assistant physicians indoctrinated in our routine.

During the entire period of the study, no other antihypertensive or diuretic therapy was administered to any patient. If maintenance digitalis was being taken this was left undisturbed. Several patients were supposedly taking a 1,000 calorie, 2 mg. salt diet and this was not altered. No potassium supplements were administered.

Serum electrolyte concentrations (sodium, potassium and chloride) were determined on at least two occasions in 21 patients. In 10 of these a determination was made on the same day that the patient started on the active drug and a second determination was carried out after 4 to 9 weeks of continuous therapy. In the remaining 11 patients the initial electrolyte determination was not made until after 1 to 4 weeks of therapy with benzydroflumethiazide and the second determination was made after a further 4 to 11 weeks of continuous therapy.

Results and Discussion

Our results in the 27 patients remaining for analysis after defaulters were eliminated are outlined in table 1. Cases are arranged in the table in descending order of baseline diastolic pressures; the figure in parentheses following each of these baseline readings indicates the number of weekly visits incorporated in the mean figure.

Effect on blood pressure. Although the diastolic blood pressure, quite rightly, is the more generally heeded pressure, there is no question that depression of high systolic pressures is also of clinical importance. Therefore, in assessing the response to medication, account should be taken of significant lowering of systolic as well as diastolic pressures. The most satisfactory formula for accomplishing this is to grade responses according to the fall in mean blood pressure (i.e., systolic + diastolic pressure divided by 2) but at the same time to impose a minimum satisfactory fall in diastolic pressure. We have regarded a *mean* fall of 15 mm. Hg. or more, provided that the diastolic fall is at least 10 mm., as the minimal satisfactory response. Thus a systolic fall of 10 accompanied by a diastolic fall of 20, or a diastolic fall of 10 accompanied by a systolic fall of 20 would each fulfill minimum requirements.

From the table it can be seen that 23 of the 27 patients (85%) achieved a fall in mean blood pressure of 17 mm. or more, all of whom had a diastolic fall of 11 mm. or more. Of these 23 "successes," 20 were unknowingly transferred to a second course of dummy

TABLE 1

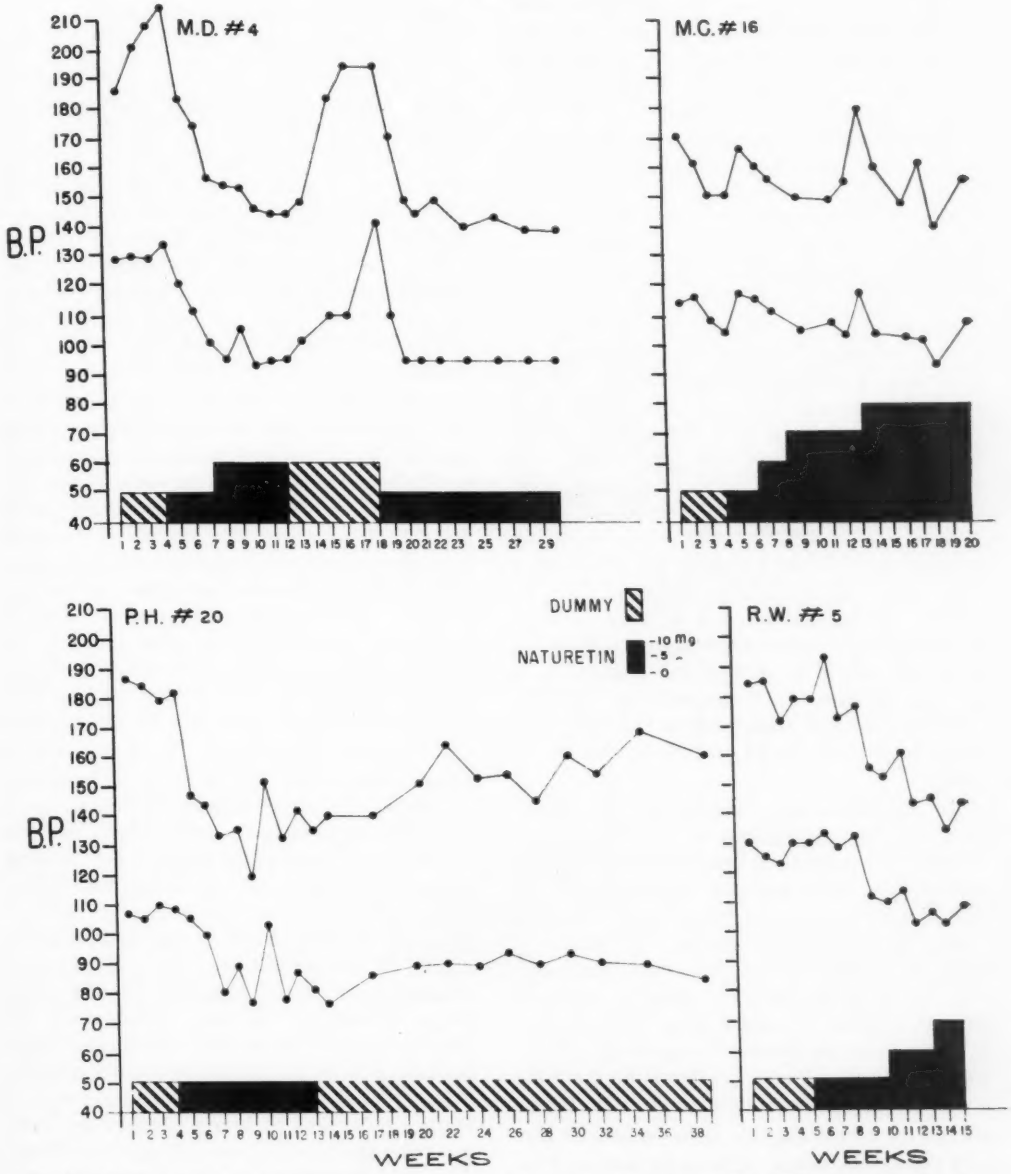
	Identification	Race and Sex	Baseline B.P. on Dummy Tablets	Mean Weight on Dummy Tablets	Mean B.P. at Last 3 Weekly Readings on the Drug	Mean Weight on the Drug	Fall in B.P. on the Drug	Fall in Mean B.P.	Weight Change in Lbs. on Drug Therapy	Maximum Daily Dose in Mg.	Maximum Return of B.P. on Repeat Dummy Tablets	After Weeks	Weight at That Time
1.	H.P.	CF	226/139 (3)	184½	163/104	166	63/35	49	—17½	40	191/111	5	167¼
2.	L.J.	CF	202/135 (3)	160	174/108	158¾	28/27	27	— 1¼	30	195/121	4	158
3.	E.T.	WF	252/134 (2)	138	204/106	135	48/28	38	— 3	40	—	—	—
4.	M.D.	WF	203/130 (4)	180¼	145/95	178	58/35	46	— 2¼	20	194/142	6	184
5.	R.W.	CM	179/128 (5)	185	142/107	178	37/21	29	— 7	30	—	—	—
6.	M.Ja	CF	194/122 (3)	175½	144/99	177½	50/23	36	+ 2	40	191/115	2	180½
7.	S.M.	WM	192/120 (5)	210½	150/103	196½	42/17	29	—14	20	189/110	3	193½
8.	S.B.	CF	185/120 (4)	153½	135/93	151	50/27	38	— 2½	10	176/114	9	149
9.	E.B.	CM	201/117 (5)	145½	154/95	147¾	47/22	34	+ 2¼	40	202/112	2	147½
10.	M.Jo	CF	176/117 (3)	147½	139/92	147	37/25	31	— ½	10	180/104	3	147¼
11.	S.V.	CF	179/115 (4)	148	139/93	147	40/22	31	— 1	20	—	—	—
12.	M.S.	CF	187/114 (3)	130¾	133/90	125¾	54/24	39	— 5	40	181/110	5	130¾
13.	E.M.	CF	167/113 (4)	192½	143/99	189	24/14	19	— 3½	30	164/111	5	196¾
14.	W.T.	WM	177/112 (4)	161½	164/111	165	13/1	7	+ 3½	40	—	—	—
15.	R.F.	CF	163/110 (4)	188	147/83	180	16/27	21	— 8	20	174/108	7	176½
16.	M.Cl	WM	159/110 (4)	191	150/99	182½	9/11	10	— 8½	40	—	—	—
17.	J.S.	WF	207/109 (7)	138¼	193/109	143¾	14/0	7	+ 5½	40	—	—	—
18.	M.O.	CF	157/109 (4)	188¼	139/92	187¾	18/17	17	— ½	40	173/110	3	191¾
19.	C.F.	WF	168/108 (4)	111	145/96	108¼	23/12	17	— 2	20	185/114	7	106¼
20.	P.H.	CF	183/107 (4)	143¾	136/82	144	47/25	36	+ ¼	10	162/83	26	133½
21.	J.F.	CF	155/106 (5)	133	149/99	135¾	6/7	6	+ 2¾	30	199/117	10	136
22.	M.Co	CF	185/105 (4)	176	146/89	171½	39/16	27	— 4½	20	183/101	6	172½
23.	M.M.	CF	152/104 (6)	189¾	132/88	184	20/16	18	— 5¾	10	185/116	4	192½
24.	E.L.	CF	187/103 (5)	156¾	158/90	152	29/13	21	— 4¾	40	176/99	6	153¾
25.	C.M.	CF	198/102 (4)	127	136/87	121¼	62/15	38	— 5¾	30	158/100	8	126½
26.	E.K.	WM	205/101 (3)	189½	175/90	177	30/11	20	—12½	20	178/88	11	183
27.	B.D.	CF	194/100 (6)	139	147/84	135	47/16	31	— 4	20	196/102	9	138¼

medication; of these 20, 18 showed a definite resurgence of blood pressure offering further confirmation of the effectiveness of the active preparation. It is noteworthy that the remaining 2 patients, (Cases 20 and 26), after 12 and 26 weeks of dummy medication respectively, continue to maintain a near normal blood pressure (Fig. 1). It is impossible to say whether this represents a lasting effect of the drug or is an indication that the observed fall in blood pressure was coincidental and not produced by the medication. In Case 20 a further complicating factor was a loss of ten and a half pounds during the 26 weeks of renewed dummy medication. If therefore one chooses to omit these two cases and the two "successes" who were not exposed to the second course of dummy tablets, there is left a total of 23 acceptable cases; satisfactory responses followed by subsequent resurgences of blood pressures on dummy medication occurred in 19, or 82%, of these.

It is worthy of note that the patients with the highest diastolic pressures (8 patients with diastolic pressures of 120 mm. or more) all manifested a gratifying response with falls in diastolic pressure ranging from 17 to 35 mm. and falls in mean pressures ranging between 28 and 49 mm. In contrast, the 4 failures all had considerably lower diastolic pressures (range 106 to 112) and 3 of the 4 were white. Indeed satisfactory responses were seen in only 5 out of a total of 8 white patients whereas 18 out of 19 negro patients responded well.

Relationship to diuresis. Some observers believe that the fall in blood pressure occasioned by the thiazide derivatives is a function of diuresis alone. We have not addressed ourselves to a study of this point, but it is our impression that there is a depressor effect independent of diuresis, and this impression is borne out by inspecting the relationship of weight change to blood pressures. The fact that a significant fall in blood pressure can occur without a significant weight loss (Cases 2, 10, 11, 18, 20), and indeed even in association with some gain in weight (Cases 6, 9), is at least suggestive evidence that

FIG. 1



Graphs of B.P. readings from 4 representative patients. No. 4 shows a typical response to benzydroflumethiazide with subsequent resurgence of both systolic and diastolic pressures during the second dummy period. No. 16 illustrates a typical failure despite increase of dosage to 40 mg. daily. No. 20, following an apparent good response to the drug, illustrates a failure of the diastolic blood pressure to rise significantly on reinstated dummy medication; the systolic pressure meanwhile appears to be rising slowly but steadily. No. 5 is one of 2 cases who were included in our over-all figures despite the fact that a second dummy period was not achieved; the graph illustrates an apparently satisfactory response to therapy but lacks the confirmation of a subsequent resurgence as shown by No. 4.

diuresis and decrease in blood pressure are not necessarily interrelated. Furthermore, during the second course of dummy medication the blood pressures in several patients rose significantly while their weights remained reduced (Cases 1, 7, 8, 15, 19, 22).

On the other hand it is certainly true that in general there is an association between loss of weight and fall in blood pressure; thus of the 23 patients who showed a significant depression of pressure, only 3 failed to lose some weight; the largest weight loss observed (17½ lbs.) was also associated with the greatest fall in blood pressure (Case 1). Conversely, 3 of the 4 patients who failed to respond with a fall in blood pressure also failed to lose weight; and of the 5 patients in whom a gain in weight was recorded, 3 failed to show a significant fall in blood pressure.

Electrolytes. In 21 patients, 2 or more serum electrolyte (sodium, potassium, chloride) determinations were made. In 10 of these pretreatment concentrations were obtained on the day that the dummy tablet was discontinued and the active drug was started. After 4 to 9 weeks of therapy, electrolyte levels were again determined. In 8 there was an increase in sodium concentration ranging from 4 to 13 mEq./L., while in 2 there was no significant change. Concurrently 5 patients showed a definite decrease in potassium concentration (range 0.46 to 1.1 mEq./L.) while 5 showed no change or a modest increase. In 9 patients the chloride concentration fell (range 0.8 to 11.7 mEq./L.) while in the remaining patient it rose by 5.1 mEq.

In the remaining 11 patients the initial electrolyte determinations were not made until after 1 to 4 weeks of benzydroflumethiazide therapy; in these patients a subsequent determination was made after a further 4 to 11 weeks of continuous therapy. Of these 11 patients, 9 showed a rise in sodium concentration of from 0.8 to 11.3 mEq./L. while 2 showed a fall of 1.2 and 7 mEq. In 3 of these 11 patients no significant change in potassium concentration was noted, whereas in 6 an increase occurred of from 0.22 to 1.36 mEq., and in the remaining 2 a decrease of 0.83 and 0.18 mEq. was noted. Chlorides fell in 7 of these 11 by from 1.1 to 12.5 mEq.; in 2 there was no significant alteration while in the remaining 2 the level rose by 5.4 and 23.4 mEq./L.

Combining these figures for the 21 patients, mean electrolyte shifts may be summarized as follows:

mean increase in sodium concentration	5.14 mEq./L.
mean increase in potassium concentration	0.007 mEq./L.
mean decrease in chloride concentration	3.16 mEq./L.

Such figures are admittedly inadequate for evaluating the influence of the drug on the electrolyte economy, but they are at least sufficient to suggest that serious electrolyte shifts are unlikely to occur with any frequency during short courses of Naturetin even in relatively high dosage. Certainly there was no significant evidence of potassium depletion in any of our cases although no potassium supplements were administered to any of them.

Dosage and side-effects. The value of increasing the dosage of benzydroflumethiazide in the control of hypertension remains to be evaluated. Some authorities believe that any effect that can be obtained with 40 mg. would have been obtained if a dosage of 10 to 20 mg. daily had been maintained. We have gained the impression, but admit that it may be false, that increasing the daily dose to 30 or 40 mg. accelerates the attainment of the desired depressor effect. Our effective dosages ranged between 10 and 40 mg. and no side-effects of any type were seen in any patients.

Long-term maintenance. It is too early to report finally on the efficacy of benzydroflumethiazide in the prolonged control of essential hypertension; nevertheless our experience with follow-up therapy on the drug for up to 30 weeks may be of interest. Of the patients who, after a satisfactory fall in blood pressure, were returned to the dummy medication for the second time and experienced a resurgence of blood pressure, 15 were once again transferred to the active drug. Of these, 9 appear to be well maintained after periods of 4 to 30 weeks; on the other hand, 5 have failed to develop or maintain a satisfactory reduction of blood pressure with the same dosage of the drug that had previously proved effective. In the one remaining patient results are so far equivocal.

It is therefore apparent that, of the patients who initially obtain a satisfactory fall in blood pressure on benzydroflumethiazide, all do not maintain this fall. The long-term efficacy of the drug remains to be properly assessed.

Summary and Conclusions

1. Forty-one patients with diastolic blood pressures over 100 mm. Hg. were selected for a single-blind study of the effectiveness of benzydroflumethiazide in essential hypertension. Pretreatment control levels (on dummy medication) of diastolic pressure ranged from 100 to 139 mm. Hg.

2. Blood pressures did not fall significantly on dummy tablets alone in any patient. Fourteen patients failed to attend regularly and were discarded from the study. Of the remaining 27 patients, 23 (85%) obtained a gratifying response, i.e., a fall in mean blood pressure ranging from 17 to 49 mm. including a diastolic fall of 11 to 35 mm. Four patients showed little or no response (mean blood pressure fall of less than 15 mm.). Dosages of the new drug ranged from 10 to 40 mg. daily.

3. Of 20 patients who were returned to a subsequent course of dummy medication, 18 manifested a significant resurgence of blood pressure, further confirming the efficacy of the active drug.

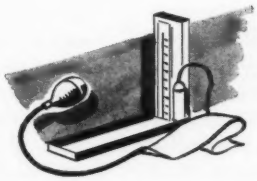
4. In the patients successfully treated, there was an inconstant correlation with concomitant weight loss suggesting that the antihypertensive action of benzydroflumethiazide is partly independent of its diuretic effect.

5. No significant dislocation of electrolytes and no clinical side-effects were observed in any patients.

6. From these results one may conclude that the drug is an effective agent in the majority of patients for the short-term control of essential hypertension. No claims for long-term maintenance can be made on the basis of this limited study. Indeed, 5 of 15 patients who initially experienced a satisfactory fall in blood pressure, in a subsequent follow-up period have already partially or completely escaped from control by the drug.

Acknowledgment

It is a pleasure to express our gratitude to Miss Ann Bacon whose contribution to the smooth and efficient execution of this study was invaluable.



Clinical Investigation of Benzydroflumethiazide in Edema and Hypertension

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As the pharmaceutical houses market their particular derivative of benzenedisulfonamide, the physician should remember that all act in the same manner in preventing reabsorption of sodium in the proximal tubule. Also that side-effects will be identical if use of the drug will have been for a sufficient length of time.

Introduction

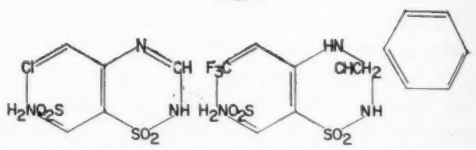
A NEW ORAL DIURETIC (3 benzyl dihydroflumethiazide) whose structural formula is compared to chlorothiazide is shown in figure 1.

Chlorothiazide, hydrochlorothiazide, flumethiazide, dihydroflumethiazide and benzydroflumethiazide (Naturetin) are all derivatives of benzenedisulfonamide. They all act on the proximal renal tubule preventing reabsorption of sodium chloride in approximately equal amounts. The effect is very similar to that seen with mercurials which also act at this site. Acetazoleamide and spirolactone act on the distal renal tubule, the former by inhibiting carbonic anhydrase and the latter by blocking aldosterone.[1]

As for the mode of action of the diuretic's hypotensive effect, Tobian[2,3] has shown that there is an increased sodium and water content in the walls of the aortas of hypertensive rats. Also diuretics have been shown to block some of the action of norepinephrine.[1] The exact mode of action, however, both as diuretic and hypotensive agents, has not been fully elucidated.

Ford,[4] in his pharmacologic investigations of diuretics, found that there is a greater increase in excretion of sodium chloride and urine with 5 mg. of benzydroflumethiazide than with 50 mg. of hydrochlorothiazide. Benzydroflumethiazide also is said to cause less loss of potassium and bicarbonate.[4] "In this respect it more closely approaches the natural or 'ideal' diuretic." He found the dosage response to be at its maximum between 2.5 mg. and 5.0 mg. with no significantly greater natruresis with the 10 mg. dose.[5]

FIG. 1



CHLOROTHIAZIDE 3 BENYL DIHYDROFLUMETHIAZIDE

Structural formulae.

Ford and associates[5,6] established the potency of chlorothiazide. He found that 1,109 mg. equals 1 cc. of meralluride. More recently he found that 2.8 mg. of benzydroflumethiazide is equal to 2 cc. of meralluride.

Friend[1] states that "benzydroflumethiazide is the most potent of the series and the most potent diuretic so far developed. Early data indicates it may soon be the diuretic of choice."

This study is a clinical investigation of benzydroflumethiazide undertaken in an effort to determine its clinical effectiveness in edema of all types, hypertension and to ascertain its toxicity.

Materials and Methods

Eighty-eight patients were taken at random from the obstetric, medical and employees' clinic at Touro Infirmary. Twenty-five white patients in the age range 14 to 41 years were selected from the obstetric clinic

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and 63 patients were selected from the medical and employees' clinic. Their ages ranged from 21 to 80 years but were predominantly in the older age group. The medical patients were further divided into those with: congestive heart failure—15 patients; congestive heart failure with hypertension—20 patients; hypertensive cardiovascular disease alone—25 patients; varicosities with edema—one patient; lupus erythematosis nephrosis—one patient; premenstrual edema—one patient. By sex and race, there were 5 white males, 33 white females, 12 colored males and 13 colored females. In the obstetric patients 2.5 mg., 5.0 mg., 10 mg. and 20 mg. were administered from 1 to 4 weeks. In the medical patients studied for edema, 2.5 mg., 5.0 mg., 10 mg. and 15 mg. were administered from 2 weeks to 3 months. In the hypertensive patients studied 2.5 mg. to 30 mg. were given from 2 weeks to 4 months.

Results

The results found in patients with obstetric type of edema are summarized in table 1. Failures were classified as any gain in weight. Two of the 3 patients were failures with benzydroflumethiazide 2.5 mg. (patients 2 and 3); 2 of 17 patients were failures with benzydroflumethiazide 5.0 mg. (patients 12 and 20); there were no failures on 10 mg. and 20 mg. of benzydroflumethiazide. Note the almost immediate rebound of weight gain on discontinuing the drug.

Five of these patients had received chlorothiazide prior to benzydroflumethiazide therapy and had gained excessive weight. Three of these had doses of 500 mg. daily and then received benzydroflumethiazide 5.0 mg. daily with resultant weight loss of 3, 4 and 5 pounds. One received chlorothiazide 1,000 mg. then benzydroflumethiazide 10 mg. with a 3 pound weight loss. One had received hydrochlorothiazide 100 mg. and 5.0 mg. benzydroflumethiazide with a one pound weight gain.

The results found in patients with a medical type of edema are summarized in tables 2 and 3. In table 2 with no prior chlorothiazide therapy, a failure was classified as any failure to lose weight. Neither of the 2 patients on 2.5 mg. failed to lose weight. Four of the 5 patients on 5.0 mg. were failures as follows: Patient 3—B.P., a neuropsychiatric patient, whose initial weight was taken after an extended depressive anorexic episode.

TABLE 1

OBSTETRIC EDEMA

PATIENT NUMBER	WEEKS 1	2	3	4
1		−1		
2				+4
3		0		+2
4	−6			
5	−5	−1	+4	
6	−1			
7	−4	0	+2	
8	−5	0		
9	−4			
10	0	+2		
11	−4			
12	+1			
13	−3			
14	−3			
15	−4	−1	+4	+9
16		−6	+5	
17		−6		−4
18			−3	0
19		−4		−3
20	+1	+4	+1	
21	−22	−7		
22	0	+3		
23	−7	−2		
24	−5			
25	−4	−3	+3	
26	−1	−2	−4	
27	−3	−7	−12	

All patients had previous excessive weight gain (a gain in excess of 2 pounds per month) when they were placed on benzydroflumethiazide. This weight was taken as zero in the graph and all the numbers are in relation to this first weight. Three patients had two separate trials of therapy. The heavy black line indicates when the drug was stopped. For example, the last patient in the graph shows that at the end of one week of 20 mg. of benzydroflumethiazide, she weighed 3 pounds less and the drug was stopped. One week later she weighed 12 pounds less than she had 3 weeks previously.

Edema and shortness of breath decreased on therapy. This patient had one month therapy of benzydroflumethiazide 2.5 mg. prior to this therapy. He is also listed as a failure in table 3; Patient 4—T.C., both acetazoleamide and mercurials were discontinued during therapy; Patient 6—F.S.G. had no detectable edema throughout course. Shortness of breath subjectively improved with therapy; Patient 7—E.B. had benzydroflumethiazide 10 mg. immediately prior to this therapy with weight loss. One of the 9 patients on benzydroflumethiazide 10 mg. was a failure as follows: Patient 14—S.B. had carcinoma of the breast which was removed one year prior to therapy with possible pulmonary metastasis as well as congestive heart failure.

In table 3 with previous chlorothiazide therapy, a failure was classified as any gain in weight. Two of the 5 patients on 2.5 mg. were failures as follows: Patient 1—B.P. is

TABLE 2

MEDICAL EDEMA
No Previous Chlorothiazide Therapy

Benzydroflumethiazide Dosage	*Pt. No.*	*Months* 1	2	3
2.5 mg.	1	−3		
(meralluride)	2	−7		−13
5.0 mg.	3	+3	+2	+4
(meralluride acetazoleamide)	4	NC		
	5	−2		
	6	NC		
	7	NC		
10 mg.	8	−4		
	9	−6		−11
(Benzydroflumethiazide 5.0 mg.)	10	NC	−2	
	11	−4		
	12	−2	−2	
	13	−5		
	14	NC	+5	+7
	15	−8		
	16	−21		

The weight of the patients when they were started on benzydroflumethiazide is taken as 0 and all subsequent changes in weight are in relation to this initial weight. Plus and minus one pound is designated no change and abbreviated NC. Medications discontinued are indicated in the left-hand column in parentheses. No other diuretics or hypotensive agents were started during this time. Two patients were digitalized soon after diuretic therapy was started and were dropped from the series. The last recorded weight indicates the length of therapy in months.

listed as Case 3 in table 2; Patient 4—R.S., edema and hypertension worsened on therapy. It should be pointed out these patients had been on chlorothiazide 500 mg. or hydrochlorothiazide 50 mg. None of the 18 patients on benzydroflumethiazide 5.0 mg., 10 mg. or 15 mg. were failures. Several had quite good results.

TABLE 3

MEDICAL EDEMA
Previous Chlorothiazide Therapy

Benzydroflumethiazide Dosage	*Pt. No.*	*Months* 1	2	3
2.5 mg.	1	+2	+9	
	2		−3	NC −7
	3		NC	
	4		+6	
	5		NC	
5.0 mg.	6		−1	
(meralluride)	7			−13
(meralluride)	8			−18
	9		+1	NC
	10		NC	
	11		NC	NC NC
	12		−1	NC
	13		NC	NC NC
	14	+1		
10 mg.	15		−2	+3 −3 NC NC
	16		NC	NC NC
	17	NC		NC NC
	18		−3	−6
	19	NC	NC	NC
	20		+4	NC
	21	+1	−3	−2
	22	−6	−17	
15 mg.	23	−9	−11	

(See also footnote on Table 2.) All patients had been on chlorothiazide 500 mg. daily for an extended period of time prior to the initiation of benzydroflumethiazide therapy. All patients seen that had previously been on chlorothiazide were changed to benzydroflumethiazide. Most of these were well controlled at the time therapy was initiated. Patient 15 had been on hydrochlorothiazide 100 mg. daily.

The results found in patients with hypertension are summarized in tables 4 and 5. For those who had no prior chlorothiazide therapy, a failure of the blood pressure to decrease was classified as a failure and for those on previous chlorothiazide therapy, any increase in blood pressure was a failure. There were no failures in the group presented in table 4 who were treated primarily for their hypertension. In those treated primarily for their edema with no other change in their antihypertensive therapy, there was one failure on 2.5 mg. Patient 1—F.S.C. had improvement in shortness of breath. There were 2 failures on 5.0 mg.: Patient 8—C.A.; Patient 10—E.B. had no improvement in edema or hypertension. There was one failure on 10 mg.,—Patient 14—M.H. who had no improvement in edema or hypertension.

In the patients who had received previous chlorothiazide therapy, represented in table 5, there was one failure on 5.0 mg. in those treated for hypertension alone: for Patient 7—T.C., reserpine was discontinued. There were no failures in the 2.5 mg. and 10 mg. groups. In the congestive heart failure groups, there were 2 failures with 2.5 mg.: Patient 5—L.P. had weakness on higher doses of benzydroflumenthiazide; Patient 6—R.S. was a failure in both edema and hypertension. There were no failures in the 5.0 mg. and 10 mg. groups.

Several patients were tried on a higher dose of benzydroflumethiazide and are summarized as follows:

Patient 1—V.W. had no prior therapy. The B.P. was reduced from 210/130 on the diuretic 15 mg. to 155/90 in one week. It was further reduced to 150/80 on 10 mg. the second week.

Patient 2—J.G. had had no prior therapy. He was started on benzydroflumethiazide and the B.P. was reduced from 190/90 to 170/80 on 15 mg. for one week and to 145/70 the second week.

Patient 3—M.B. had no prior therapy. He was started on reserpine 0.25 mg. twice daily and benzydroflumethiazide 10 mg. The B.P. fell from 240/115 to 170/90 in one week. The dosage was then increased to 20 mg. for 3 weeks with no change. The dosage was then increased to 30 mg. and the B.P. fell to 135/70 in 2 weeks. At this time the patient was found to have an asymptomatic right ureteral calculus with right-sided calycectasis. History revealed very mild right flank pain for several months prior to therapy.

Patient 4—J.H. had prior therapy of reserpine 0.25

TABLE 4

HYPERTENSION
No Previous Chlorothiazide Therapy

Benzydroflumethiazide Dosage	*Pt. No.*	*Months* 1	2	3	
2.5 mg. (H.C.V.D.)	1	+10/+15			
	2	—25/—30			
5.0 mg. (H.C.V.D.)	3	—55/—10			
	4	NC	NC	—25/—20	—25/—20
(C.H.F.) & (H.C.V.D.)	5	—30/—35	—40/—35		
	6	—20/0			
	7	—90/—25	—50/—15		
	8	—40/0	0/+6		
	9	0/—10			
	10	NC	NC		
10.0 mg. (H.C.V.D.)	11	—50/—15	—85/—40	—80/—50	
	12	—70/—20			
	13	—40/—15			
	14	—20/0			
	15	—55/—30			
	16	—50/—10			—30/—20
(C.H.F.) & (H.C.V.D.)	17	NC			
	18		—20/—10		
	19	—70/—60	—30/—15		

Hypertensive patients were divided primarily into those who had received previous chlorothiazide (chlorothiazide 500 mg. per day or hydrochlorothiazide 50 mg. per day) and those who had received none. Secondarily they were treated after being divided into those patients who had only hypertension and those who were treated primarily for their edema with accompanying hypertension. The blood pressure at the time of initiation of therapy was taken as the baseline and all subsequent recordings are in relation to this baseline. If the blood pressure was found to fluctuate on a constant regimen prior to therapy, a mean blood pressure was taken as the baseline. Plus or minus 10 mm. of mercury systolic and 5 mm. of mercury diastolic was classified as no change and designated as NC. Six patients had courses of therapy on two different doses of the drug.

TABLE 5

HYPERTENSION
Previous Chlorothiazide Therapy

Benzydroflumethiazide Dosage	*Pt. No.*	*Months* 1	2	3
2.5 mg. (H.C.V.D.)	1		—30/—10	
	2		NC	
	3	NC	NC	
	4	NC	NC	
(C.H.F.) & (H.C.V.D.)	5		+70/+10	+50/+20
	6	+20/0		
5.0 mg. (H.C.V.D.)	7	0/+20		
	8	0/+20	—25/0	—15/0
	9	NC	NC	
	10	NC		
	11	NC		
	12	0/—14	NC	
(C.H.F.) & (H.C.V.D.)	13		NC	NC —30/—20
	14	NC		
	15	NC	NC	
	16	—10/—10	—20/—10	—20/—10 —20/—10
	17		NC	NC
10.0 mg. (H.C.V.D.)	18	—30/—10		
	19	NC		
	20	—30/0	—5/—15	NC
	21	NC	—25/—15	
	22			NC
(C.H.F.) & (H.C.V.D.)	23	NC	NC	0/+10 NC
	24	+20/+15		—20/—15 —10/—10
	25	+30/+20	NC	
	26	+10/+10 —20/0		NC —30/—10
	27	NC		
	28	—30/0	—10/+10	—30/0

(See footnote on Table 4.)

mg. twice daily. The B.P. was reduced from 200/130 to 180/100 on benzydroflumethiazide 20 mg. for 3 weeks. Reserpine was discontinued for 2 weeks with a rise in B.P. to its previous level of 200/130.

Patient 5—G.E., a 30 year old negress, having hypertension of several years duration, was on a therapeutic regimen of reserpine 0.25 mg. 4 times daily, pentolinium tartrate 120 mg. daily, chlorothiazide 500 mg. daily, promazine hydrochloride 50 mg. twice daily. Her B.P. remained 220/140. It was reduced to 210/125 on 5.0 mg. of benzydroflumethiazide for one month, the chlorothiazide, pentolinium tartrate, and promazine hydrochloride having been discontinued. On 10 mg. of benzydroflumethiazide for 2 weeks, the blood pressure was reduced to 200/130. Benzydroflumethiazide 20 mg. was then given for one week which reduced the blood pressure to 185/115. Then 30 mg. of benzydrofluthemiazide was given for 2 weeks which resulted in a B.P. of 170/105. She was tried on 40 mg. for one week with a resultant fullness in her forehead on stooping. At this point she ran out of medicine and did not return to the clinic for several weeks at which time the B.P. had returned to its previous high. She was then put on benzydroflumethiazide 30 mg. and reserpine 0.25 mg. 3 times daily for 2 weeks with no reduction in blood pressure.

Toxicity

In the obstetric group, 17 of the 25 patients delivered during the time of the study. All infants were normal except for one infant who had mild erythroblastosis and whose mother had a past history of erythroblastosis fetalis. One patient discontinued the medicine because of vomiting and diarrhea. She had, however, nausea and vomiting, headache and backache during the whole course of her pregnancy. Another thought the pills nauseated her. They were discontinued then and recontinued one week later with no nausea.

In the hypertensive group studied, the patients that were found to have side-effects from benzydroflumethiazide are as follows: Patient 1—A.C. discontinued benzydroflumethiazide 5.0 mg. because it made her "weak"; Patient 3—V.W. had nausea that subsided after 2 days on continued therapy; Patient 4—E.R., a diabetic, previously con-

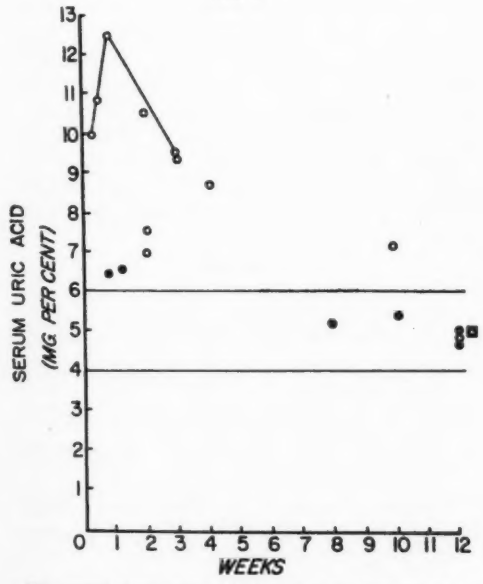
trolled tolbutamide, took benzydroflumethiazide 5.0 mg. daily for 5 months. The fasting blood sugar rose from 110 mg. % to 190 mg. % in this interval.

In the congestive heart failure series, the patients who were found to have side-effects from benzydroflumethiazide were as follow: Patient 5—L.P. had nausea, dizziness and weakness on benzydroflumethiazide 5.0 mg. a day; Patient 6—H.S. was operated on for gastrointestinal bleeding of intermittent nature for 9 months, and died of surgical complications. Patient 7—M.S. died with acute pyelonephritis, renal and congestive heart failure; the electrolytes were normal. Patient 8—A.R. discontinued the drug because of acute auricular fibrillation; Patient 9—L.F. died in congestive heart failure; Patient 10—E.B. died from liver failure and uremia.

No evidence of skin rashes, bone marrow depression, pruritis, or other toxic symptoms were found in any of the group. Blood sugars were not determined on the nondiabetic patients. No attacks of gout were observed.

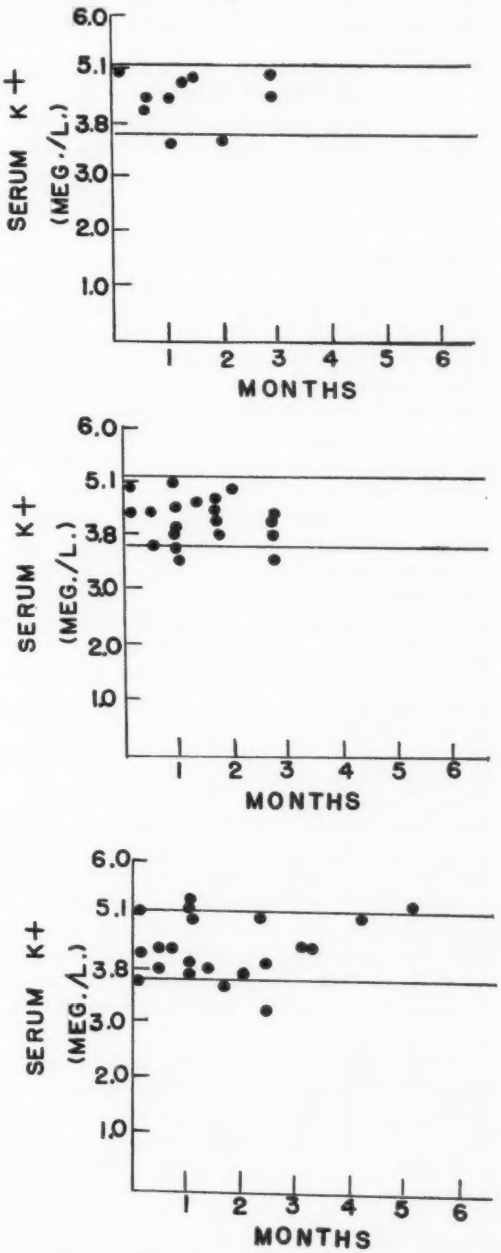
Determinations of serum uric acid were made on several obstetric patients and a number of medical patients, and were found to be generally elevated shortly after initiation of therapy as evidenced in figure 2. Note the

FIG. 2



The normal serum uric acid of 4 to 6 mg. per 100 ml. is represented by two parallel lines. (Serum uric acid was not determined before therapy.) Solid dots represent 5 mg. doses and circles represent 10 mg. doses. The circles connected by a line represent one patient. The other dots and circles are scattered readings on different patients. The circle in the square was taken at 5 months.

FIG. 3



Normal serum potassium levels of 3.8 to 5.1 mEq./L. are included by the parallel lines. Results of medication with benzydroflumethiazide are shown: (top) 2.5 mg. dosage, (center) 5 mg., and (bottom) 10 mg.

higher values obtained with 10 mg. doses.

Levels of serum potassium were determined intermittently on a number of the medical patients. The scatter graphs (Fig. 3) indicate the potassium levels in relation to dosage and time.

Discussions of Results

In the obstetrical patients an excellent result was obtained. With the 5.0 mg. dose, the average weight loss recorded was 3 pounds a week and the 10 mg. dose, 6.5 pounds per week.

As a diuretic in the medical patients, good to excellent results were obtained in the 2.5 mg. and 10 mg. group while poor results were obtained in the 5.0 mg. group. In the group that had been on prior chlorothiazide (500 mg. daily) therapy, good results were obtained in the 5.0 mg. and 10 mg. groups. Poor results were obtained in the 2.5 mg. group that had previously been on chlorothiazide 500 mg. daily.

As a hypotensive agent, a good to excellent result was obtained in the group treated for hypertension alone while the group that was treated primarily for edema had several failures. However, in the group that had previously been on chlorothiazide 500 mg. daily or hydrochlorothiazide 50 mg. daily, it compared favorably except in the 2.5 mg. group. It might be noted here that in those patients in whom the drug failed as a diuretic, it also failed as an antihypertensive. Several patients were tried with doses up to 30 mg. with good results and no side-effects. We believe our findings indicate as Ford stated that there is a greater diuresis with 5.0 mg. of benzydroflumethiazide than with hydrochlorothiazide 50 mg. or chlorothiazide 500 mg.[4-6] We attributed the better diuresis with the 10.0 mg. daily dosage to the fact that the doses were staggered 5.0 mg. in the morning and afternoon.

In this study a rather low toxicity was found with nausea and vomiting, weakness, diarrhea and a fullness referred to the forehead at the 40 mg. dosage comprising the complaints. There were 4 deaths. None were thought to be related to the drug. One diabetic had a rise in the fasting blood sugar.

Serum uric acids were elevated in most cases except on prolonged (months) administration. Siegal and Dubin[7] found that it was impossible to follow the course of their eclampsia patients on chlorothiazide therapy by the use of serum uric acids because of their generalized elevation while on the drug. We must conclude from our findings that this is also true of benzydroflumethiazide.

Serum potassiums were found to be within normal limits in most cases but lower than normal in some, especially on higher doses of the drug. No cases of clinical electrolyte imbalance were encountered.

Summary

Twenty-five obstetric patients and 63 medical patients were given a clinical trial of benzydroflumethiazide, a new oral diuretic agent, using a 2.5 mg. to 30 mg. doses. This represents 67 patients with edema of which 11 were failures as follows: 4 of 10 patients on 2.5 mg.; 6 of 32 patients on 5.0 mg.; 1 of 23 patients on 10.0 mg.; and none with 2 patients on 15 mg. and 20 mg. This also represented 52 hypertensive patients of which 7 were failures as follows: 3 of 8 patients on 2.5 mg.; 3 of 19 on 5.0 mg.; and 1 of 20 on 10.0 mg. doses. Five hypertensive patients were tried on higher doses up to 30 mg. with good results. Toxic effects included mild nausea and vomiting, weakness, mild diarrhea and a fullness in the forehead at 40 mg. doses, elevated serum uric acids, decreased serum potassiums (usually within the normal range). No cases of clinical electrolyte imbalance were encountered.

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Ulcerative Colitis*

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One of the enigmas of medicine is the entity of ulcerative colitis. Until its etiology and pathogenesis are established, its management must remain symptomatic. Surgery plays its part in some of these cases. The author, from long experience in this field, offers his thoughts on this facet of management.

Introduction

I TAKE IT as a great privilege and honor to be a guest speaker before this meeting of the Surgical Section of the Southern Medical Association.

My choice of a topic was influenced by the fact that we have had an unusual experience at our hospital in the surgical treatment of ulcerative colitis. This experience is attributable in great part to the interest that Dr. Henry W. Cave, formerly chief of our surgical service, developed in the disease. His enthusiasm and the courage he gave these patients, combined with his skill and charm, attracted more and more of them to our institution as the years passed.

Clinical Considerations

A total of 440 patients suffering from ulcerative colitis were admitted to the hospital during the 25 year period beginning with 1934. Of these, 203 of them were operated upon, and underwent a total of 337 surgical procedures—many being "multiple-staged" operations (Table 1).

Before proceeding to the main topic of my discussion, which is the surgical treatment and, in particular, some of the problems presented by the ileostomy, I would like to make a few observations about the disease which have a background interest.

We know today that ulcerative colitis is more or less world-wide, and does not seem to favor any particular nationality or ethnic group. Similarly, climate is not a significant factor influencing its onset, unless one would attach importance to the fact that the disease is more common in the northern than in the southern part of the United States.

TABLE 1

ULCERATIVE COLITIS
1934-1959

Total number of patients admitted	440
Total number of patients operated upon	203
Total number of operative procedures	337

To cover the etiology of the disease is to dismiss it with the simple remark that it still remains unknown. The clinical picture is usually that of a patient who has suffered weeks or months of diarrhea, who may or may not give a history of a definite onset with a specific bowel infection. The patient may or may not be in a state of poor nutrition, depending entirely upon the phase or duration of the disease. However, to make a definite diagnosis, there must be demonstrable ulceration or suppurative changes in the bowel wall, and in reaching this decision we rely upon the barium enema and the sigmoidoscope.

Age of onset. Although the onset of ulcerative colitis has been historically fixed to the general ages of 20 to 40, our experience would indicate that the age limits run from 10 to 60 (Table 2).

TABLE 2

AGE OF ONSET OF DISEASE IN 390 PATIENTS
(Unrecorded in 50 of 440 Patients Admitted)

Age in Years	*Patients*		*Sex*	
	Number	*Per Cent*	*Male*	*Female*
Under 10	14	3	5	9
10-19	106	28	57	49
20-29	119	32	61	58
30-39	81	20	38	43
40-49	37	9	17	20
50-59	21	5	13	8
60 and over	12	3	4	8
Total	390	100	195	195

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In the typical case the disease begins in the rectum, and then gradually extends proximally until it involves the remainder of the colon. This does not always hold true, since patients are encountered in whom the rectum does not appear to be affected. In a few the disease remains confined to the left colon or to the right colon, or it may be located in scattered or segmental areas throughout the large bowel. In the latter case one should be alert to the fact that segmental areas of ileitis may also exist. It is thus evident that the disease does not always follow a consistent pattern of involvement.

It was with this segmental and localized variety of the disease that we were tempted, early in our experience, to try more conservative resections with primary or secondary anastomosis. Unfortunately, they proved uniformly unsuccessful, undoubtedly due to the fact that the remaining large bowel, though grossly normal, was microscopically involved.

In trying to simplify the indications for surgical intervention in our patients, it can be stated that it was *"to preserve and prolong life."* Either because the patient was undergoing an acute fulminating episode from which we feared he might not recover, or was in such a debilitated state from the chronic ravages of his disease, we believed an acute exacerbation might prove fatal. Needless to say, most of the patients had associated complications, some of which made surgery even more urgent.

Complications. The development of complications quite naturally affects the prognosis and darkens the outlook for recovery. Since ulcerative colitis is a disease of long chronicity, these complications may be varied (Table 3). They may arise in the *gastrointestinal tract,* as abscesses, fistulas, hemorrhage from the bowel wall (resulting in secondary anemia), perforation of the colon into the free peritoneal cavity, frank strictures of the bowel, polyposis, and carcinoma. *Systemic complications* are also frequent, due to the lack of proper physiologic functioning over a long period. Important among these are anemia, hypoproteinemia, electrolyte imbalance, liver disease, arthritis, cutaneous lesions (such as pyoderma gangrenosum), and thrombophlebitis. Table 4 demonstrates how often we encountered some of the more troublesome systemic complications. The development of arthritis should be considered an indication for elective surgical eradication of the disease before the joint changes become permanently crippling.

TABLE 3

ASSOCIATED GASTROINTESTINAL COMPLICATIONS IN 440 PATIENTS

	Number of Cases	*Incidence*
Pseudopolyposis	102	25%
Anorectal (Perirectal abscess, fistula-in-ano, fissure, and hemorrhoids)	72	17
Ileitis	38	9
Malignancy of colon	15	4
Rectovaginal fistula	11	3
Perforation of the bowel	14	3
Pericolic abscess	10	2.5
Generalized peritonitis	8	2
Massive hemorrhage	6	1.5

Treatment

The initial treatment of all our patients was medical, and this is as it should be, regardless of whether or not surgery is being contemplated. In preparing patients for operation, strict attention to correction of the fluid and electrolyte imbalance is of paramount importance; in addition, they are frequently deficient in minerals—in particular iron and calcium—and these should be replenished.

There is no doubt that corticotropin and the adrenal steroid hormones have been effective in suppressing and ameliorating the symptoms. They may even induce a remission in the acute fulminating form of the disease. There is no concrete evidence, however, that these endocrine agents are curative or that they will ultimately alter the final outcome of the disease. I mention this fact

TABLE 4

ASSOCIATED SYSTEMIC COMPLICATIONS IN 440 PATIENTS

	Number of Cases
Arthritis	15
Urinary tract calculi	7
Severe dermatitis	5
Severe nephritis	5
Thrombophlebitis	4
Diabetes	4
Infectious hepatitis	4
Cirrhosis	3
Pulmonary tuberculosis	3

because most of our surgical patients in recent years have come to us from our medical confreres after many months of treatment with the steroids. Nearly all of them have been in the acute fulminating stage, some with impending perforation, and are usually presented to us as desperate operative risks, frequently verging on adrenal exhaustion. The steroid replacement during the operation and in the immediate postoperative period has added to our problems.

At this point in my discussion I would like to simplify the classification of these patients by placing them in two general categories. First the so-called "chronic" ones. These are the patients that have probably suffered for years, are intractable to medical therapy, do not have a septic temperature and are likely to be good or fair surgical risks.

The second type is the patient with an acute (or fulminant) form of the disease. This is the individual who has a septic temperature, is almost continually at stool, is losing considerable blood from his bowel, may present the threat of perforation of the colon, and is a *desperate* surgical risk.

Early in our experience we used ileostomy alone, as a first stage procedure for both the acute and the chronic stages of the disease. If the patient survived, we proceeded to a second, third, or even a fourth stage procedure, removing, successively, segments of diseased colon.

Early surgical treatment. Table 5 is comprised mainly of patients treated early in our experience, shows the operative mortality for the patients who had ileostomy alone, and the mortality in those who had ileostomy as a first stage to be followed by one or more subsequent procedures. What this table does not reveal is that the mortality in those suffering from the acute fulminating form of ulcerative colitis was approximately 70 per cent.

During the first 10 years, our efforts were continually directed toward lowering the mortality and improving the results. Eventually certain important facts became evident. Outstanding among these was the realization that ileostomy alone proved to be of no benefit to these patients. It added a needless preliminary stage for those in the chronic phase, and did little or nothing to improve the status of the patient in the acute phase, should he be lucky enough to survive the insult inflicted upon him.

TABLE 5

THE EARLY SURGICAL APPROACH TO TREATMENT OF THE DISEASE

	Number of Cases	*Deaths*	*Mortality*
Ileostomy alone (No further surgery)	27	15*	55%
Ileostomy at first stage (Followed by multiple procedures to remove diseased colon)	78	11	14
Total	105	27	25.7%

*All deaths were of patients in acute fulminating stage.

As we embarked on a policy of combining ileostomy with a partial colectomy of that portion of the colon most seriously affected, our mortality began to drop. We even indulged in some fancy types of operating, such as making an ileostomy, and excising for example, the badly diseased descending colon, and then creating three mucous fistulas that communicated with the remaining disfunctioned portions of the large bowel. These segments deprived of their function were often thought to be doubtfully affected by disease, but by putting them at rest we hoped that a safe "hook-up" would be successful at a later date.

It gradually became apparent that the more diseased the portion of the colon was and which we removed initially at the time an ileostomy was formed, the less toxic was the patient during the immediate postoperative period. Finally, we were combining ileostomy with subtotal colectomy in one stage. When the remaining rectum was diseased, it was removed by abdominoperineal resection as a second stage procedure. In the past 10 years, 35 patients, many of them in the acute stage, have been treated in this fashion. There have been 3 deaths, an overall mortality rate of 8.5 per cent.

It was believed that continued toxicity from residual disease in the remaining rectum had played an important part in the fatal outcome in the 3 patients who died after combined ileostomy and subtotal colectomy, as they had all been in the acute fulminant phase.

We were inclined to believe that an ileostomy and total proctocolectomy in one stage would lower the operative mortality in similar

cases, by immediately removing the entire source of their sepsis.

The major problem we faced with these very sick patients was to minimize the operative shock attending a procedure of this magnitude. We believe our experience during the past few years demonstrates that shock *can* be successfully overcome when such an operation is performed under hypothermia at the level of 90°F. Six of our acutely ill patients have had total ablation of their disease in this manner, and all of them survived. *All* were critically ill at the time they were subjected to surgery, and it is my firm belief that most if not *all* would have succumbed, had we treated them, as we did in the early days, by ileostomy alone.

We have also learned to our sorrow, over a period of years, that proximal colectomy with ileosigmoidostomy is not a good operation for those patients whose disease seems confined to the proximal colon. Our follow-up on 17 cases revealed it to be almost universally unsuccessful. A more *limited* experience with proximal colectomy and ileoproctostomy has been equally discouraging. An added danger to this type of "hook-up" is the threat of ascending ileitis coincident with recrudescence of disease in the remaining colon or rectum.

On the other hand, we recommend colostomy with preservation of apparently unaffected proximal colon when the disease seems limited to the distal colon. Although some of these patients may eventually develop disease in their proximal colon, and need a secondary procedure, the majority of *our* patients still have their original colostomy.

Figure 1 represents the exception. It represents the barium study of a patient who had a distal colectomy and an abdominoperineal resection 22 years ago. He recently showed evidence of disease in his retained ascending colon, and last summer I removed his remaining bowel (along with his gallbladder) and performed an ileostomy.

In attempting to simplify for you the surgical approach to ulcerative colitis, we believe the following procedures can be recommended.

(1) An ileostomy and total proctocolectomy in one stage, where the entire colon and rectum is involved. If the patient is in the acute fulminant phase, the procedure should be performed under hypothermia.

FIG. 1

Barium enema through a midtransverse colon colostomy shows a very contracted and diseased residual right colon. (Note also the gallbladder filled with small calcified stones, presenting the density one might expect to find after cholangiography.)

(2) When only the distal colon is involved, a proximal transverse colostomy, and a distal proctocolectomy in one stage is recommended.

(3) Where only the proximal colon is involved, the extent of involvement will influence the treatment. If only the ascending colon seems to be diseased, it is reasonably safe to excise the ascending colon, and then to perform an ileotransverse colostomy. However, if the ascending and transverse colon are both involved it is safer to perform an ileostomy and then to remove all of the proximal colon down to the sigmoid, and bring out its distal end as a mucous fistula.

The patient and surgeon alike are always hopeful in these instances that a hook-up between ileum and sigmoid may eventually be affected. I must reiterate that our experience has been most disillusioning. With a lapse of time our patients have usually demonstrated residual disease in the sigmoid and rec-

tum that required an abdominoperineal resection; for this reason an ileosigmoidostomy has usually been disastrous.

Reference should be made at this point to the relationship between ulcerative colitis and carcinoma of the colon. The incidence of carcinoma in the 203 surgical patients in our series was 8 per cent. There is little doubt that the longer ulcerative colitis persists in the colon, the greater is the chance that a malignant change will develop. Many patients with extensive untreated disease will undoubtedly die of toxemia or the other complications of ulcerative colitis before malignancy can manifest itself. However, there is increasing evidence that patients with residual diseased colon, whose lives have been prolonged by ileostomy will develop cancer in the unremoved segment in at least 25% of the cases. In other words, carcinoma will develop in one out of four patients who live long enough with extensive disease in the colon or rectum.

This threat of malignancy emphasizes the importance of periodic check-up examinations on the patient who has an ileostomy, and who has not had the colon or rectum completely removed. The persistence of disease in the retained bowel represents a constant menace to his life.

Complications of Surgery

There is no question that in the earlier days when we were using ileostomy alone, or the multiple stage procedures in the treatment of the disease, these patients were the *sickest* and presented the most complicated postoperative abdominal problems in our hospital. The actual surgical complications were *legion*. Massive hemorrhage, perforation, intestinal fistulas, generalized peritonitis,—everything one could dream of in his worst nightmare, in addition to the more usual complications that one might, for example, expect to encounter after the average procedure on the stomach or gallbladder.

Since adopting the *one stage procedure* for removing all the diseased colon, the immediate postoperative complications in these patients have more nearly approached the average for abdominal operations of all types.

In the *early* postoperative period, at least two thirds of the complications have borne some relationship to the construction of the ileostomy. Dysfunction of the stoma can be one of the most worrisome. The stoma rarely, if ever, begins to function before the third postoperative day, and normally when it begins the discharge is watery, bile-stained intestinal fluid which takes a few days to begin to thicken noticeably. In some the ileostomy may discharge so profusely as to create a serious electrolyte imbalance. In others the opposite situation exists with only an occasional expulsion of gas and ileal contents, and with cramping abdominal pains, creating the suspicion of an impending obstruction. Under the latter circumstances a large Levine tube passed proximally through the ileostomy may relieve a mechanical kink, and result in its correction so the stoma will behave normally.

A most distressing and troublesome early postoperative complication is the development of extensive excoriation of the skin. The best treatment for this condition is its prevention, and this can be accomplished by good nursing care.

In fact, many complications related to the ileostomy can be minimized, if not completely avoided, by following certain principles in its original construction as well as in its care after the operation has been completed.

The location of the stoma is of great importance since the flange of the ileostomy bag must be ideally placed. In the early postoperative period, when a temporary disposable bag is used, the spine of ilium, the umbilicus, and the exploratory incision are the 3 hazards to its efficient use. It is necessary to provide easy access to the bag when changes are necessary, and to allow them to be accomplished without disturbing or contaminating the main wound. The area of skin around the stoma should be smooth and wide enough to insure a good flat surface, so efficient cohesion of skin to the glue on the bag will occur. Such a location is even more important to the patient from the moment he begins to wear his permanent appliance. The flange of his bag cannot efficiently seal off the stoma if it abuts against the spine of the ilium or the umbilicus, and it must not be placed so low as to hamper him when sitting down.

In general, we believe the ideal location for the ileostomy is a point midway between the

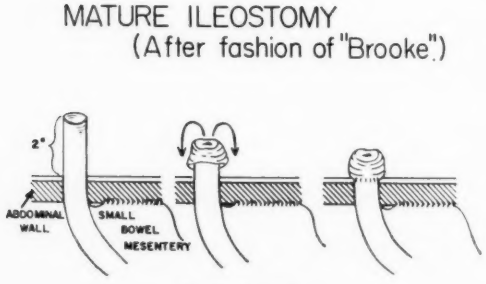
right anterior superior spine and the umbilicus. We also recommend that the colectomy be performed through a left paramedian incision.

The technical construction of the *ileostomy* is of great importance in lessening the more serious postoperative complications (Fig. 2). We excise a button of skin at the predetermined location in the right lower quadrant, incise the anterior rectus sheath, split the underlying muscle, and open the peritoneum. The ileum is then brought out through this opening so as to protrude at least two inches beyond the skin level. While held exteriorized to this extent, the mesentery of ileum is tacked upward to the peritoneum of the anterior abdominal wall in the direction of the falciform ligament, for a distance of about two inches. We believe this discourages vovulus or torsion, and minimizes the later danger of prolapse.

When the exploratory abdominal incision has been closed, the clamp is removed from the ileum; its opened end is then everted and sutured with a continuous "lock-stitch" of fine plain catgut to the circular skin opening. This is called the "Brooke" ileostomy, and it immediately presents a "matured" appearance. After dressing and "sealing off" the main exploratory incision, a temporary transparent disposable ileostomy bag is glued in place over the stoma.

Once the stoma begins to function, the bag should be emptied at frequent intervals. The body movements of patient in bed, and the weight of accumulated contents in the bag constantly threaten to loosen the adherent surface which is protecting the healthy skin. Once leakage occurs beneath the "seal," it is of paramount importance to remove the bag, thoroughly cleanse and prepare the skin, and attach a new appliance. Otherwise, the irritating effects of the stomal discharge can make the skin "raw" overnight.

FIG. 2



Brooke ileostomy.

TABLE 6

IMPORTANT LATE COMPLICATIONS IN 203 PATIENTS WHICH REQUIRED RE-OPERATION

	Number of Cases	*Incidence*
Obstruction	16	9%
Prolapse	15	8
Stomal fistula	10	8
Ascending ileitis	6	3
Stricture	5	3

Once true excoriation of the skin develops it can be treated most effectively with Karaya gum powder sprinkled generously over the area, and also applied to the flange of the permanent ileostomy bag. The powder combines healing qualities with a strong adherent effect that discourages leakage. A mixture of Karaya gum powder and unflavored Amphogel can be similarly used. This method of treating excoriation cannot be accomplished with a temporary appliance, and for this reason it is wise to measure for, and order a permanent ileostomy bag and have it on hand before the operation is performed.

The *late* complications associated with the formation of the ileostomy will be mentioned in order of their frequency (Table 6).

(1) *Intestinal obstruction.* This may be due to an adhesive band but not uncommonly we find a volvulus or an incarceration of gut about the limb of ileum which is forming the ileostomy. On several occasions this has produced the "maypole" effect. The incidence of late obstruction in our series has been 9 per cent.

(2) *Prolapse* has been another distressing late complication, and when irreducible or recurrent, it requires operative revision. As some patients tend to develop recurrence of the phenomena after revision, one should strongly consider at the second operation a "Nobel" type of "plication" of the distal 12 inches of ileum, up to the point where it enters the abdominal wall. Eight per cent of our patients developed prolapse.

(3) *Stomal fistula formation* has occurred in 5% of our patients. The fistula may originate superficially in the stoma, or may be more deeply placed within the abdominal wall so that it has had to burrow outward to establish a communication with the skin. We believe

these fistulas are encouraged by the following mistakes in technic: The use of any sutures in the wall of the ileum as it passes through the abdominal layers; any form of postoperative intubation of the stoma; and, finally, any attempt to dilate the ileostomy digitally. Since adopting the "Brooke" technic of forming the stoma we have had no fistulas. A not uncommon cause of superficial fistula formation is encroachment of the opening of the ileostomy bag on the stoma, with resulting pressure effects and erosion.

Other less common late complications are stenosis and retraction of the stoma, recession of the mucosa of the ileostomy, ascending ileitis proximal to the ileostomy, and finally, herniation adjoining the ileostomy stoma.

Although these patients can be rehabilitated to a state of normal nutrition and activity, and in most instances can live a perfectly normal life, they are always living with, and threatened by, the handicaps imposed by the ileostomy.

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Variation of Standard Technics for Correction of Blepharoptosis*

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The author reviews several technics for the correction of this abnormality, and indicates the circumstances which determine the choice of the type of procedure.

THAT THERE ARE MORE THAN EIGHTY TYPES of operations for ptosis indicates the wide variety of methods available for correction of blepharoptosis.[1] These methods are usually classified according to whether levator, frontalis or superior rectus muscles are used. Levator resection has the great advantage of permitting almost normal blinking and synchronous following movements of the lid with the eye. Usually, in congenital or acquired ptosis with levator action present, levator resection methods give the best cosmetic and functional result, unless jaw winking is prominent.

In my experience, the most satisfactory technic of levator resection has been block resection of the levator and conjunctiva performed by the conjunctival route,[2-4] similar to that described by Iliff.[5] The technic of block resection of levator and conjunctiva by the conjunctival route is shown in figure 1, A to F. Application of the ptosis clamp (Fig. 1, B and C) permits easy dissection of the levator muscle along natural tissue planes from the orbital septum and other lid structures and reduces bleeding by clamping the tarsal arcades. Tedious dissection of the conjunctiva is avoided since the levator muscle, Müller's muscle, and conjunctiva are dissected as one layer from the other lid structures. Sutures rarely pull through this more sturdy layer (Fig. 1, D and F) as compared with a sometimes flimsy layer of levator muscle alone. In cases of poor levator action, when a large section of the levator and conjunctiva is resected, shortening of the conjunctiva may produce strength from the attachments of the superior rectus muscle to increase apparent levator action through the transition of superior rectus action.

Variations in Technic of Block Resection of Levator and Conjunctiva

During the past 6 years, a number of variations in technic have been incorporated into the procedure of combined levator-conjunctival resection from that originally described by Iliff.[5]

(1) *Amount of Resection.* First, the most important variation to keep in mind from the original description of the Iliff operation (which specified a 13 mm. levator resection) is to vary the amount of levator resection as indicated. In congenital ptosis, a large amount of levator resection is usually necessary to be assured of adequate correction. This is because the levator muscle in congenital ptosis is partly replaced by connective tissue, and a large amount of levator muscle must be resected to assure sufficient correction.[3,6] If the history is reliable and confirms a congenital etiology, an average of 13 mm. of combined levator-conjunctival resection will usually be required (Table 1). Less extensive resection (11 mm.) may be necessary in mild ptosis of 2 to 3 mm. with good levator action. In congenital ptosis of moderate degree with only fair levator action, a minimum of 13 mm. to 15 mm. of levator resection should be performed. In severe congenital ptosis with only poor levator action, 16 to 18 mm. or more of total resection of the levator, conjunctiva, and tarsus should be done. One must remember that the chances of overcorrection in congenital ptosis are minimal, particularly with more severe degree of ptosis and with decreasing amounts of levator action. The main problem with congenital

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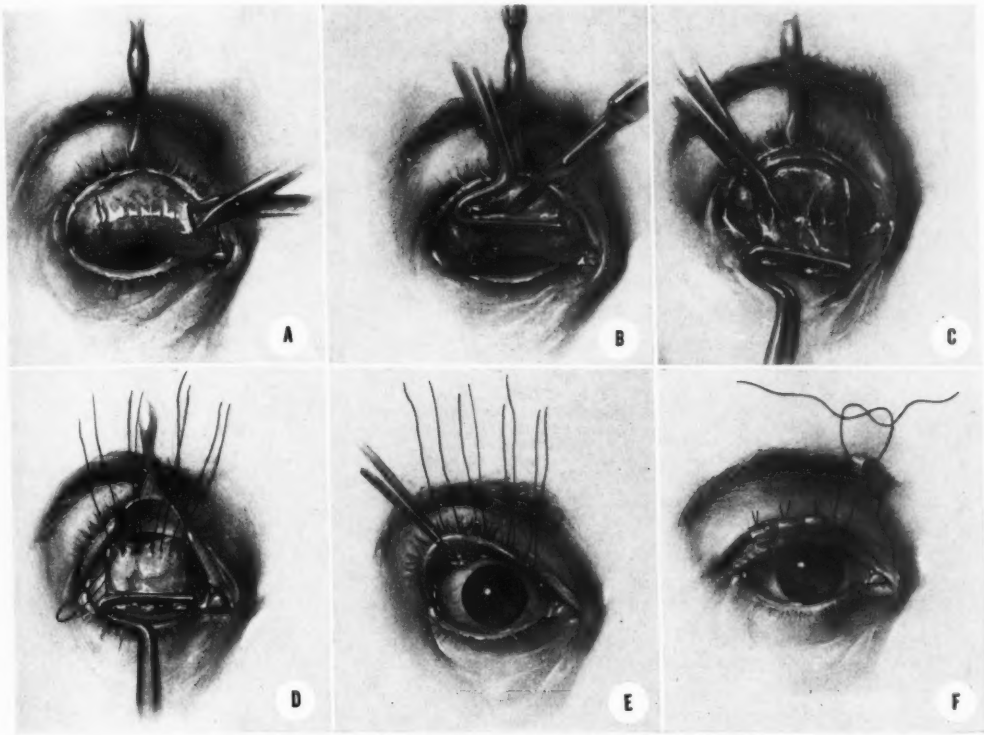
FIG. 1



(From Schimek and Cusick[3] by permission of the Am. J. Ophth.) (A) The upper lid has been everted with a lid holder. With sharp-pointed scissors, buttonhole incisions are made medial and lateral to the superior edge of the tarsus to enter the potential space between the upper segment of the tarsus and the skin. (B) One jaw of a Berke ptosis clamp has been passed into the temporal buttonhole, passed across the lid between tarsus and skin and out through the nasal buttonhole. The jaws are clamped together. An incision is made distal to the clamp through the tarsus close to its upper border. (C) By sharp and blunt dissection, the levator, Müller's muscle and the conjunctiva are separated as one layer from the lid and septum orbitale toward the level of the fornix. (D) Four double-armed sutures are then passed through the layer of conjunctiva, Müller's muscle, and levator at the desired distance from the free border. Excision is performed 2 mm. in front of the suture line. (E) The sutures are passed through the lid anterior to the tarsus to emerge about 3 to 4 mm. above the lash line and are tied. (F) The sutures may be looped through and over cut sections of rubber catheter and tied.

ptosis is the high incidence of under-correction. This is illustrated in table 2, which shows the results in my early experience from 1954 to 1957 before more extensive levator resection was undertaken in congenital ptosis to compensate for its tendency to under-correction. By contrast, in patients with acquired ptosis, who have good levator action, only small amounts of levator resection, such as 6 to 8 mm. should be performed. Here, the levator muscle has much more potential corrective power when shortened, in contrast with congenital ptosis in which much of the muscle structure is replaced by nonfunctioning scar tissue.[6] In Horner's syndrome (persisting longer than one year), where the levator muscle itself is normal and only Müller's muscle is affected, usually a 5 mm. resection will be sufficient. Caution in detecting acquired ptosis as opposed to congenital ptosis, by accurate history, and performance of less extensive resection in acquired senile ptosis and larger resections in congenital ptosis, will pay rich dividends in good results.

(2) *Amount of Dissection.* The extent of levator resection will usually control how much dissection of the levator is necessary. If much more than 13 mm. of levator and conjunctival tissue is resected, the medial and lateral horns usually must be cut. The greater the amount of levator resection, the more completely the layer of levator-conjunctival tissue must be dissected from the lid structures. With less than 13 mm. of levator

TABLE 1

SUGGESTED AMOUNTS OF LEVATOR -CONJUNCTIVAL RESECTION

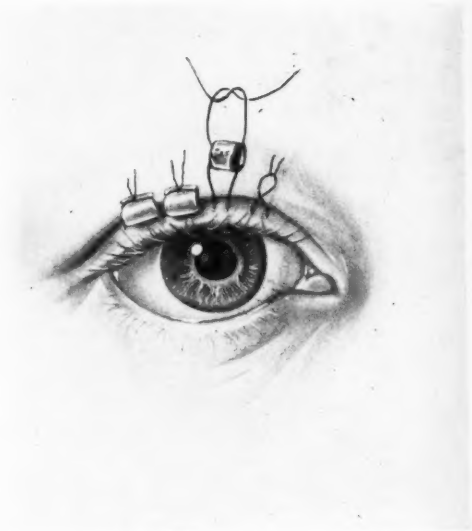
Congenital ptosis of:	
Mild degree (2-3 mm.)* and with good levator action (8 mm. or more)**	10 to 12 mm.
Moderate degree (4-6 mm.) and with fair levator action (3-7 mm.)	13 to 15 mm.
Severe degree (7 mm. and more) and with poor levator action (2 mm. or less)	16 to 18 mm. or more
Acquired ptosis of:	
Horner's syndrome	3 to 5 mm.
"Senile hereditary" (depending on degree of ptosis and levator action)	6 to 8 mm.
Traumatic—fresh laceration	reattachment
Traumatic—old laceration	reattachment with 5 to 7 mm. resection
Traumatic—blunt injury (if good levator action present)	6 to 8 mm.

The grouping of mild degrees of congenital ptosis with good levator action and vice versa is useful for orientation. From a clinical viewpoint, often one must approximate the amount of levator resection directly with the degree of ptosis and inversely with the levator action as two separate variables, and consider many other influences such as blepharophimosis.

*Measure the primary position by comparing the ptotic lid-level with the normal lid-level, and by estimating the vertical diameter of the cornea as 11 mm.

**Immobilize frontalis, place a mm. ruler in front of lids and with gaze directed up and down, estimate the maximum upper lid movement in millimeters.

FIG. 2



The two lateral levator muscle sutures have been looped through and tied over cut sections of rubber catheter. The middle nasal suture is shown with each arm passing through the cut section of rubber catheter and looped over it with a knot being tied. The most nasal suture shows the length of suture available if the section of rubber catheter is cut and removed but the suture is left tied. This length of suture can be allowed to retract into the lid giving a semblance of controlled recession of the levator muscle.

resected, extensive dissection and cutting of the levator horns is either optional or unnecessary.

(3) *"Controlled" Relaxation of Sutures in Case of Over-correction.* Figure 1, F shows the levator sutures passing through a cut section of rubber tubing. Each suture on emerging from the lid is looped through each section of rubber tubing (each of the double-armed needles is passed through the piece of tubing in opposite directions) and tied over it. Figure 2 shows another view of the sutures passing through such a piece of rubber tubing and being tied over it. The most nasal suture (Fig. 2) shows the excess suture material which would remain available for retraction into the lid if the rubber catheter section is cut out without cutting the sutures themselves. If over-correction occurs in the first 2 or 3 days after operation, the section of rubber catheter can be cut and removed without cutting the surrounding suture. The 6 mm. (approximately) of extra suture length thus obtained can be allowed to retract into the lid, particularly if the patient massages downward and the surgeon tugs on the lid border. Since the suture is still attached and knotted, the levator muscle cannot become completely detached. This technic permits a

TABLE 2

Type of Ptosis	*No. Cases*	*Excellent*	*Good*		*Poor*	
			Slight Under-correction	*Slight Over-correction*	*Considerable Under-correction*	*Considerable Over-correction*
Congenital	97	64 (66%)	9 (9%)	2 (2%)	22 (23%)	0 (0%)
Acquired hereditary (nontraumatic)	10	2 (20%)	1 (10%)	4 (40%)	0 (0%)	3 (30%)
Acquired traumatic	8	4 (50%)	1 (12%)	0 (0%)	1 (12%)	2 (26%)

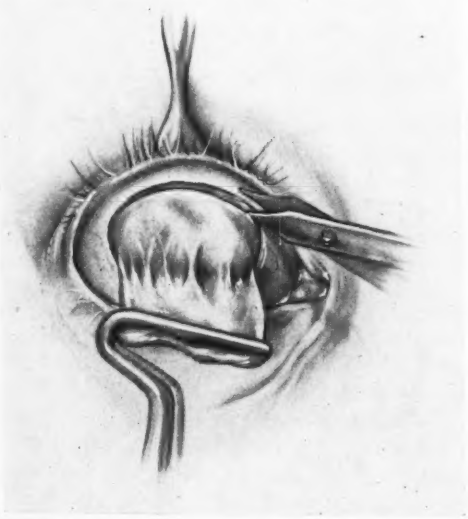
(From Schimek, R., and Cusick, P.[3] by permission of the Am. J. Ophth.) Previous results of 115 modified Blaskovics operations based on the Iliff technic, during the years 1954-1957. Since then, the percentage of under-corrections in congenital ptosis has been lowered by resecting larger amounts of levator. The percentage of over-corrections in acquired ptosis has been lowered by resecting smaller amounts of levator.

semblance of controlled levator recession without operative interference.

If there is appreciable over-correction after healing has become firmer, the lid can be turned and the tarsus incised 1 mm. from its upper edge, parallel with the lid margin, until the tarsal wound gapes two or three times the amount of over-correction present.[4] An intermarginal suture is placed between the lids to hold the upper lid down for at least 5 to 7 days. This latter procedure of Berke is necessary when more firm healing has occurred, 4, 5 or more days after operation.

(4) *Increasing the Effectiveness of a Given Amount of Levator Resection.* The following variations in technic will increase the effectiveness of a given amount of levator resection. Figure 3 shows an additional resection of the tarsus being performed with scissors. A layer of tarsus is easily dissected from the overlying orbicularis and skin with blunt dissection by scissors before the eliptical wedge of tarsus is cut. This will require greater advancement of the levator and conjunctival layer to the cut edge of tarsus and thus increase the effectiveness of the given levator resection. It is necessary to perform this additional tarsal resection only in patients requiring a large resection, as for example with 17 to 18 mm. of combined levator and tarsal resection. Figure 1, E shows both arms of the double-armed sutures from the levator muscle passing anterior to the cut edge of tarsus between the layer of tarsus and the layer of skin and orbicularis and emerging a few millimeters above the lashes. Although this is not accentuated to where conjunctiva is pulled underneath the tarsal plate, it does tuck in a fold of the levator between the cut edge of tarsus and the overlying orbicularis and skin, and thus tends to bring the levator muscle further forward, increasing the effect of the resection.

FIG. 3



An additional wedge of the tarsus can be cut to advance the levator muscle effectively and increase the effect of the levator resection.

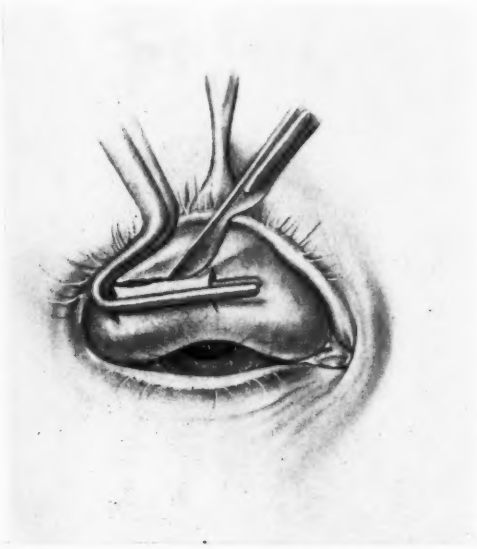
Another variation for increasing the effectiveness of levator resection is oblique passage of the needles of the double-armed sutures through the levator muscle so the sutures are passing slightly more distal through the conjunctiva and slightly more proximal through the stump of the levator muscle itself. The same effect can be produced with catgut sutures if a bite is made through the levator muscle just beneath the conjunctiva and the catgut suture is knotted about the muscle.

(5) *Segmental Resection of a Portion of the Levator.* A small perforating injury through the upper eyelid may cut a small area of the levator attachment to the tarsus. This can result in ptosis, which affects only the nasal half or the temporal half of the lid. In my series, injuries of this type have resulted from operation, ski-pole injuries, and small knife wounds. If the unaffected half of the lid is at a normal level and only the affected half is ptosed, it is reasonable to operate only on the section of levator muscle in the affected portion of the lid. Good levator action should be present in this affected portion of the lid. Buttonhole incisions through the levator and conjunctiva somewhat above the tarsus are made in the half of the lid that is drooping. In this situation, the levator muscle is usually not retracted any great distance from its normal insertion to the tarsus. The portion of the levator muscle is usually grasped in the clamp, or else found and identified, a small amount resected, and reattached to the tarsus without disturbing the half of the lid that is at a normal level. Figure 4 shows the technic of such a segmental resection of the levator muscle.

(6) *Repair for Damaged Portion of the*

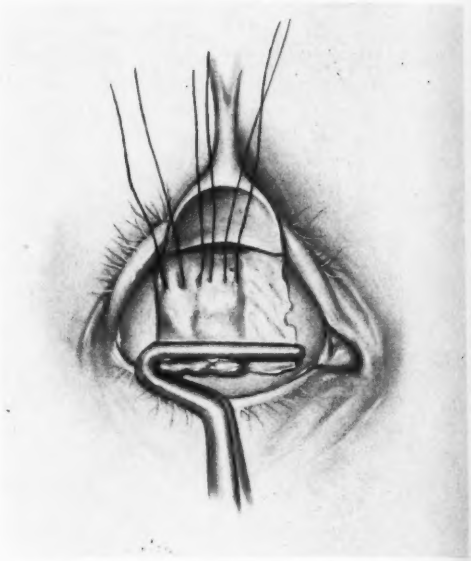
Levator Muscle. In some acquired cases of ptosis, a portion of the levator muscle will be completely destroyed and replaced by scar tissue. Figure 5 shows such a situation, in which the medial third of the levator muscle was completely scarred and atrophic without any semblance of levator muscle structure. In this instance, the scarred remnants of fibrous bands in the affected portion of the levator muscle can be resected, excised and discarded, and the remainder of fairly normal levator muscle can be resected and fanned out to attach to the tarsal border to achieve a good cosmetic result. My only example of the latter situation was a woman in whom, 30 years ago, several operations had been performed on the inner portion of the right upper eyelid to "section a nerve because of recurrent and severe pain above the right eye." Ptosis resulted, apparently from incising the medial portion of the levator muscle. Several operations were then unsuccessfully performed to reattach this portion of the levator to the tarsus. At the time I operated, about 20 years later, the medial third of the levator was completely replaced by scarred bands, which were dissected out and discarded. The remaining good levator muscle was resected and then reattached along the entire tarsal margin. The excellent cosmetic result is shown in figure 6, A and B.

FIG. 4



Resection of one half of the levator muscle, which can be done in cases in which an old injury has detached only a portion of the levator. The temporal half is being resected and reattached to the tarsus here.

FIG. 5



Scar tissue deformation totally replacing the medial third of the levator muscle. Here the remaining normal levator muscle was resected and spread out to attach along the entire tarsal margin. The scarred area of levator shown occupying the inner third of the levator was dissected out and discarded.

(7) *Repair by Conjunctival Route After More Extensive Disinsertion of Levator from the Tarsus.* Apart from the main insertion to the tarsus, the levator has attachments to the skin and conjunctiva. Even if most of the levator insertion has been cut as the result of trauma, it is usually possible to regrasp the levator with a clamp by the conjunctival route. This is only true if levator action is still present so one can be confident that some of the levator attachments are still intact. Vertical conjunctival incisions can be extended up into the fornix from the tarsal border. This is considerably above where the usual conjunctival buttonhole incisions would be placed. It is true that once the muscle clamp has been introduced into one incision and out of the other, it is best not to have the lid doubly everted and forcibly retracted as an attempt is made to grasp the muscle. After the muscle is grasped, it can be isolated in the usual way, similar to the Iliff technic, a small amount resected and then re-

FIG. 6

A B

(A) Preoperative appearance of a patient with extensive trauma and scarring to the medial part of levator with resulting ptosis of the right upper lid. (B) Postoperative appearance after the section of normal levator was resected and then spread out and reattached along the entire tarsal border. The scarred portion of the levator was discarded.

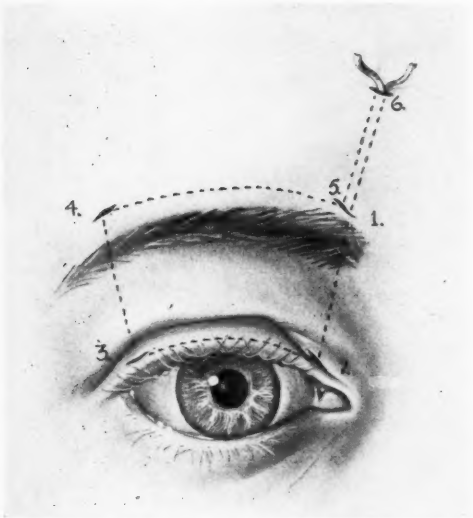
attached to the tarsus to correct the ptosis. It is surprising with what ease this conjunctival approach was used in such cases. It should be emphasized that these cases had some levator action persisting.

A Variation in the Friedenwald-Guyton Suture Operation

Some years ago, the Friedenwald-Guyton[7] suture operation was one of the favorite technics for ptosis surgery because of its simplicity and excellent initial results. Now it has been abandoned by many surgeons because of difficulty with, (1) late infections occurring along the suture tract, (2) breaking of the buried suture, and (3) slipping of the suture.

The disadvantages of the suture breaking, and of infection can be largely overcome through the use of a long strip of fascia which can easily be obtained from the leg. Crawford[8] has outlined the method for obtaining the fascial strip. Through a 2 inch incision lateral and above the knee, a strip of fascia in excess of 7 inches can be easily obtained. This strip of fascia can then be placed in the manner of a Friedenwald-Guyton suture, or with the additional modification as described in figure 7. Most ophthalmologists are familiar with the method of placing a Friedenwald-Guyton suture. Two incisions are made above the brow and 2 incisions close to the lid border as in figure 7. The strip of fascia can be placed with a three-eighths inch curved cutting needle or with a Wright fascia needle. The fascial strip is passed deeply in the aponeurosis of the frontalis muscle above the brow, and superficially in the dermis in the portion running along the lid border, as recommended by Guyton to decrease slipping. An

FIG. 7



Fascial strip from leg used as a buried ptosis suture. To minimize postoperative slipping, the fascia is passed above the brow deeply through the frontalis tendon, and along the lid border superficially in the dermis (or deeply close to or in the superficial tarsus). The fascia strips are tied at the nasal brow incision (5) with a #000 chromic suture beneath and tied about each of the two fascia knots. Then one limb of the suture is passed superficial and another deep to a higher forehead incision (6). The fascia is again tied twice, with chromic catgut tied around each knot. Modified Frost sutures (through the lower lid) should be used to protect the cornea.

additional incision in the forehead is made 2 or 3 inches above the medial brow incision as shown in figure 7. The two strips of fascia are first tied at the nasal brow incision (#5 in Fig. 7) in the following manner: A piece of #000 chromic suture is placed beneath the strips of fascia and the first knot is tied, and the chromic suture double tied about this to prevent slipping. The second knot in the fascia is tied and the same chromic suture is triple tied about it to prevent slipping. The two strips of fascia are then passed up in separate paths (one strip superficially, another strip deeply through the frontalis tendon) to emerge from the upper brow incision. The fascia strips are again tied in a similar manner and secured with catgut. The fascia strips must be tied so that the ptosis is over-corrected about 2 or 3 mm. at the time of operation. Over-correction is particularly important in unilateral ptosis because the patient does not habitually use his frontalis to hold the lid up. In bilateral ptosis, most patients will be habitual users of the frontalis and can usually compensate for mild degrees of under-correction from slipping of the suture.

Summary

Variations of a standard operative technic for ptosis are often desirable to achieve the best result for individual cases. The following variations have been described on a method of levator resection (combined levator-conjunctival resection by the conjunctival route): (1) variation of the amount of the levator resection; (2) variation of the amount of the levator dissection; (3) variations to increase the effectiveness of a given amount of levator resection; (4) compensation for over-correction by use of readjustable sutures through removable rubber catheter sections; (5) resection of a segment of the levator for any injury localized to a small portion of the levator insertion; (6) compensation for destruction of a portion of the levator muscle by use of the remaining normal levator muscle; and (7) the conjunctival approach for the correction of a traumatic disinsertion of the levator. A useful variation of a frontalis operation is also described. This concerns the use of a fascia strip placed in the manner of a Friedenwald-Guyton suture, with an additional modification.

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CASE REPORT

A Complication of Circumcision:

Probable Cause, Treatment, Results, and Legal Ramifications

THOMAS J. BAKER, M.D., and MANUEL A. GONZALEZ, M.D.,†
Miami, Fla.

A 26 YEAR OLD COLORED MAN was first examined by us approximately 14 days following circumcision. The operation had been performed by another physician.

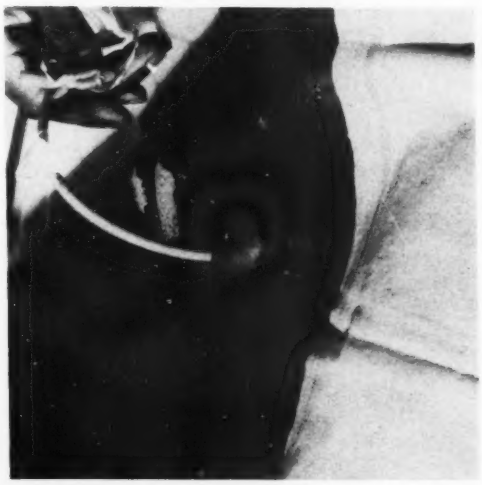
On reviewing the salient points of the history, the conclusion was that following circumcision there was considerable tension along the suture line with resultant separation of the wound. He returned to his first physician and, according to the patient, an attempt was made to reapproximate the skin margins.

Initial examination at the time we first saw the patient revealed the condition as shown in figure 1. Very little normal skin of the shaft remained—only about 2 cm. The epithelial surface in the coronal area appeared to be under considerable tension, and granulation tissue was present where the suture line had separated. Obviously there was a shortage of skin lining the shaft, and the supposition was that an excessive amount had been removed.

FIG. 1

Appearance at the time of initial examination by the authors. Note deficiency of skin on the shaft and granulation tissue at suture line.

FIG. 2



First dressing on the fifth postoperative day with complete take of the graft.

Treatment

The treatment was to recreate the defect and replace the missing skin. Under general anesthesia the original suture line, just proximal to the corona, was reopened and the shaft of the penis was allowed to stretch out to its original length. The amount of missing skin could then be seen to be between 2½ and 3 inches. An intermediate split-thickness skin graft was removed from the thigh with a Padgett-Hood dermatome and utilized to resurface the penis. The graft was held in position by suturing it to the normal skin at

†From the Department of Surgery, University of Miami School of Medicine, Miami, Fla.

FIG. 3

Condition 18 months following operation. The skin is smooth, and relatively little scarring is present. The junction of graft and skin of the shaft is seen near base of the penis.

each margin of the defect, proximally and distally. The sutures were left long and tied over the dressing in the form of a stent. The penis was further immobilized with an indwelling catheter and a large bulky elastoplast dressing.

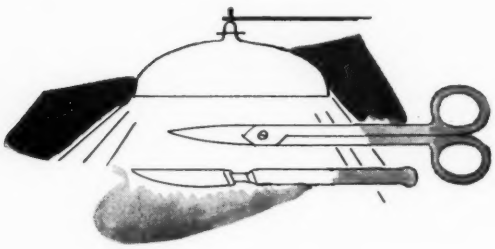
The graft was first dressed on the fifth postoperative day and the "take" was nearly perfect (Fig. 2). The patient remained in the hospital for 17 days, after which time he was seen on an outpatient basis.

Follow-up examination one and a half years following operation reveals the skin graft to have adapted well to its new environment (Fig. 3). The skin is soft, freely movable on its underlying surface, and sensation is nearly normal. He has normal erections without sacrifice of length or deviation in the direction of the shaft. Intercourse is reportedly satisfactory according to the patient and his wife.

The legal situation which evolved was expected. Litigation was initiated by the patient and, following a trial by jury, judgment against the original physician was handed down and the insurance carrier paid the settlement as directed by the court.

Summary

A case of excessive loss of skin from the shaft of the penis following circumcision is presented. The treatment, follow-up, and legal sequelae are briefly discussed.



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EDITORIAL

IODISM

A recent report upon *Iodide "Mumps"*[1] called attention to reactions to iodine both from its use in contrast media for urography as well as in oral medication. Statements were made concerning the relationship of dosage to iodism, as, "Iodism of some type will occur in most patients if a sufficiently large dose of iodides is given," and "The two cases reported are unusual because of the symptoms (parotitis) and rapid onset after small doses of iodides."

These statements were a reminder of experiences with the use of iodine, the varied reactions to its use and the idiosyncrasies in terms of dosage. Comment on iodine is worthwhile not only because of the incorporation of iodine in urographic media, but also because it may be "hidden" in both "name" pharmaceuticals and in proprietary cough and "asthma" remedies, available to the consumer over the drugstore counter. We have emphasized over and over, that a *Medication History* is as important a part of the history as the System Review these days, to uncover either iatrogenic or self-induced disease by medication.

Courtois, a French chemist, isolated iodine from seaweed exactly one and a half centuries ago. Prout, an English chemist, suggested to Elliotson, a surgeon, its use in the treatment of goiter; he used it thus in St. Thomas' Hospital in 1819. Boussingault, a French physician, suggested iodized salt in the diet for the prevention of goiter in 1833. Wallace of Dublin introduced iodide in the treatment of syphilis a hundred years ago. This with mercury represented treatment for syphilis for over a half century. Even after the introduction of arsphenamine iodine remained a part of standard treatment for late syphilis, until penicillin became available for general use. The resolution of the syphilitic gumma and quick relief of pain, as in gumma of bone, explained its routine use in the treatment of late syphilis, for the resolution of the granulomatous reaction to permit better penetration by bismuth and arsenic, and avoidance of Herxheimer reactions.

Thus, syphilologists prescribed enormous quantities of iodides. In our Syphilis Clinic, where the peak admission rate was more than 200 late or late latent cases per month, almost all were treated with metal therapy, and always with potassium iodide 0.65 to 1.6 Gm. 3 times daily for weeks to months.[2] The opportunity to observe the effects of iodide medication in some thousands of patients offered examples to illustrate the vagaries of reactions to this drug.

Iodine is rapidly and almost completely absorbed from the gastrointestinal tract, and excretion is complete in 3 or 4 days. Its immediate excretion, after absorption, by the salivary glands is attested to by the rapid recognition of a metallic taste. (To the uninitiated this point is recommended in history-taking when searching for a "hidden" source of intoxication.) The most common complaints, not of sensitization, however, are those of hyperacidity and epigastric burning due to the irritating effect of iodine upon the gastric mucosa, partially controlled by its administration at meal time or after meals. (Some iodine is excreted in the stomach.) The reactions due to sensitivity are of more interest and may puzzle the clinician.

Most common are coryza and conjunctival injection accompanied often by some edema of the eyelids. A more serious and fortunately less common degree of this is a "serum sickness type" of reaction, with edema of the tongue, lips, larynx and swelling of the joints. (After two such alarming instances in the early days of intratracheal instillation of iodized oil, which has an extremely slow rate of excretion, it was my custom to test with iodides orally for some days before bronchography.) Eosinophilia may accompany this type of reaction. Rich[3] reported the ultimate degree of this type of reaction following several days of Lugol's solution, with eosinophilia of 22% and death, and the postmortem

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findings of periarteritis nodosa. The cutaneous manifestations of iodism may be an erythema or urticaria; more commonly as in bromidism, the lesions may be acneiform, less commonly verrucose or fungating. Persistent fever and wasting, a rare form of intoxication, was often not recognized to be due to the persistent use of iodides, and proven by a reversal of the clinical picture upon discontinuance of treatment.

Occasionally, one encounters the patient who has aching referred to the parotid glands, and less commonly with subjective and objective evidence of swelling of the salivary glands. Moore[4] thought these instances not uncommon, though Stokes,[5] also with an extensive experience as a syphilologist, believed this to be rare. "Iodide mumps" has been described after a urographic medium given intravenously, and by editorial comment.[6,7]

Much is still to be known about iodism. Both Moore[4] and Stokes[5] pointed to the paradox that reactions such as coryza and acne seemed more likely to occur after initial small doses rather than large ones, and that such reactions might well disappear under the graduated increasing dosage as was recommended by some. Moore made this same point with reference to the parotitis. These experiences explain the initiation of iodide therapy with the large doses mentioned above, in the syphilis clinics where the drug was given to hundreds of patients. Nevertheless, one dose not infrequently initiates the whole train of reaction. Our Syphilis Clinic was held in the afternoon. The first prescribed dose of iodide was taken at suppertime. I well recall the number of times the house officer in the Emergency Room called in the late evening or in the night hours for advice about a patient, or seeing a patient the next morning in the Medical Clinic, led in with eyes swollen shut, edema of lips, face and tongue and stridulous breathing. These represented reactions to a single dose of probably 0.4 to 1.2 Gm. of the element.

The most remarkable instance of parotid sensitivity to iodine appeared in a middle-aged salesman who was referred for consultation because of recurrent swelling of the parotid gland. The history revealed that on his week-ends at home he was served with large steaks which he literally almost covered with salt. Since the swelling of the salivary glands, which interfered to some extent with swallowing, occurred only on week-ends at home, the iodine of iodized salt was suspected. The use of C.P. (chemically pure) sodium chloride for a few week-ends with freedom from symptoms, and their recurrence after the use of commercial table salt was recommenced seemed to bear out the surmise that the iodine of iodized salt was the cause of the swelling of the salivary glands.

Reactions to drugs are worthy of considera tion in many clinical situations.

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7. Editorial: Iodide Mumps, New England J. Med. 255:445, 1956.

25 YEARS AGO

It was just a little over a quarter of a century ago that Dr. Thomas Parran, as Commissioner of Health for New York State, had the vision of controlling syphilis by epidemiologic methods. Immediately thereafter, as Surgeon-General of the U. S. Public Health Service, he implemented this vision on a nationwide basis that resulted in an amazing reduction in the incidence of acute syphilis even before penicillin was introduced to make the task easier.—Editor.

Public Health Control of Syphilis*

"As one after another of the epidemic diseases has declined or disappeared under the impact of public health effort, it is natural that the same technics should be directed against other major causes of sickness and death. Moreover the success of past and current public health measures has engendered the confidence of the tax-paying public which will support extension of community action into fields heretofore reserved to private effort.

"These two facts make it inevitable that the public health control of syphilis should be the central problem now faced by health departments. . . .

Extent of the Syphilis Problem

"From the mass of conflicting statistics and state-

*Parran, Thomas, Jr.: Public Health Control of Syphilis, Ann. Int. Med. 10:65, 1936.

ments about syphilis, it is difficult to sort out dependable facts. This is due both to the nature of the disease and the different methods of stating its extent. Syphilis often is a subclinical infection with an unrecognized onset. It has periods of latency, and the end-point or cure frequently cannot be determined. Both the past and the present true attack rates are still the subject of conjecture. Although it shortens the life span of its victims, the total effect on mortality is not known. . . .

"In spite of knowledge concerning syphilis, which seems adequate for control, we must not lose sight of certain biologic facts which make the problem difficult: the obscure nature and transitory character of the initial lesion; the tendency of the disease to relapse under inadequate treatment; the possibility of second and completely blind infections; the unknown role of the chronic carrier as a factor in spread; and the possible reversion of the organism to a more virulent form. These factors are important and need further study. Since our present methods do not appear to have brought about a decline in syphilis prevalence, it is fair to ask if we have neglected to use to best advantage all available weapons.

Epidemiological Approach

"During recent years, the studies of Munson in New York and of Smith and Brumfield in Virginia demonstrate clearly that, by the use of the epidemiological method, undiscovered sources of infection can be found and brought under treatment. Evidence has accumulated also which shows that syphilis does not spread evenly in the population, but that it is kept alive and spreads chiefly by a series of small epidemics. . . . In the epidemiological method, we have an unused instrument for the control of syphilis which, in my opinion, is of as much value as the Wassermann test or the arsphenamines.

New York Program

"Before starting our program, it was discussed with the Public Health Committee of the State Medical Society, and many details worked out with the advice of its members. As finally agreed upon, it was approved by this committee and the Executive Committee of the State Society.

"Our syphilis control program has four major objectives: (1) The notification of cases; (2) intensive and complete investigation and supervision of sources of infection, cases and contacts; (3) the provision of facilities for adequate diagnosis and treatment; (4) professional and public education. . . .

". . . The newspapers, and recently the National Broadcasting Company have permitted the word syphilis to be used. Health departments and physicians must seize the opportunity and be prepared to furnish needed information. Yes, the word *syphilis* must be spoken, heard, printed, understood.

Summary

"The prevalence of syphilis in the United States continues to be high, and its control is the most urgent public health task with which health authorities are confronted.

"The Scandinavian countries, and Sweden in particular, by organized national effort have accomplished a modern miracle in medicine: the practical eradication of syphilis.

"The epidemiological method of locating infectious sources is an unused weapon, but potentially as valuable as the arsphenamines and serodiagnosis.

"New York State is undertaking a serious state-wide control program with full cooperation of the medical profession.

"What the health department is doing in New York can and should be done in every State. . . ."

ERRATUM

In the March issue, in the article by Dr. Frank J. Curran, "Progress in Certification of Child Psychiatrists," page 287, paragraph "The Committee . . . ," line "the Secretary . . . ," the date for applications for certification on record should be on or before September 21, 1961, instead of April 26, 1962.

SOUTHERN MEDICAL NEWS

State News Items

The Kick-Off Conference for the 55th Annual Meeting of Southern Medical Association was held in Dallas, May 19, in the French Room at the Adolphus Hotel.

Dr. Charles Max Cole, General Chairman on Arrangements, and Dr. James A. Hallmark, Vice-General Chairman, outlined duties to some 25 committee chairmen. Council members and other officers also attended the planning session.

Host societies for the Meeting—to be held November 6-9 in Dallas—are the Dallas County Medical Society, Dallas, and the Tarrant County Medical Society, Fort Worth.

Chairmen of the local committees on arrangements are: Dr. L. S. Thompson, Entertainment; Dr. J. Harold Cheek, Scientific Exhibits; Dr. Robert K. Portman, Registration and Membership; Dr. B. C. Halley, Jr., Golf; Dr. Minnie L. Maffett, Women Physicians; Dr. Cecil G. Yarbrough, Television; Dr. Milford O. Rouse, Advisory; and Mr. Millard J. Heath, Publicity.

The 21 section host committee chairmen are: Dr. William C. Grater, Allergy; Dr. Charles C. Tandy, Anesthesiology; Dr. D. Shelton Blair, Dermatology and

Syphilology; Dr. F. Clark Douglas, Gastroenterology; Dr. E. R. Cox, General Practice; Dr. Stewart A. Fish, Gynecology; Dr. Robert J. Potts, Industrial Medicine; Dr. Leonard J. Flohr, Medicine; Dr. James K. Peden, Neurology and Psychiatry; Dr. James T. Downs, Obstetrics; Dr. Claude D. Winborn, Ophthalmology and Otolaryngology; Dr. Harold A. Mattson, Orthopedic and Traumatic Surgery; Dr. C. T. Ashworth, Pathology; Dr. Hugh W. S. Powers, Pediatrics; Dr. Edward M. Krusen, Jr., Physical Medicine and Rehabilitation; Dr. Willard C. Sellman, Jr., Plastic and Reconstructive Surgery; Dr. George A. Gray, Preventive Medicine; Dr. Alvin Baldwin, Proctology; Dr. J. E. Miller, Radiology; Dr. LeRoy J. Kleinsasser, Surgery; and Dr. Ken Mooney, Urology.

The 1961 Scientific Session of the American Cancer Society will be held at the Biltmore Hotel in New York City, Oct. 23 and 24, 1961. The topic will be "The Physician and the Total Care of the Cancer Patient." For further information write Professional Education Section, American Cancer Society, 521 West 57th Street, New York 19, New York.

Research progress in projects sponsored by the Easter Seal Research Foundation will take the spotlight at the 1961 annual convention of the National Society for Crippled Children and Adults, Nov. 17-21 at the Denver-Hilton Hotel, Denver, Colorado. For more details, contact the National Society for Crippled Children and Adults, 2023 West Ogden Avenue, Chicago 12, Illinois.

The Editors of *Modern Medical Monographs* announce the 1961 competition for unpublished manuscripts on clinical subjects in the field of internal medicine. The purposes of these annual awards are to stimulate young physicians to communicate their work in the classical form of the monograph and to achieve high standards of medical writing, to further their professional reputations, and to reap possible financial rewards. For the rules for submitting a manuscript, write Dr. Irving S. Wright, 450 East 69th Street, New York 21, New York.

ALABAMA

Dr. J. F. A. McManus, Birmingham, member of the Editorial Board of the *Southern Medical Journal*, is Vice-President of the American Society for Experimental Pathology.

Dr. John W. Simpson, Birmingham, is the new President of the Medical Association of the State of Alabama.

Dr. John L. Hinton, Birmingham, is a new member of the Jefferson County Medical Society.

Dr. J. Michaelson, Foley, is Chairman of the Board of Directors of the American Academy of General Practice.

Dr. William D. Bennett, Montgomery, is President of the Alabama Chapter of the American Society of Anesthesiologists. Other officers include Dr. Arnold F. Harris, Mobile, President-Elect; and Dr. Robert W. Grady, Fairfield, Secretary-Treasurer.

Officers of the Alabama Academy of Ophthalmology and Otolaryngology are Dr. Paul S. Mertins, Montgomery, President; Dr. Joseph M. Dixon, Birmingham, Vice-President; and Dr. Carl B. Denkwith, Montgomery, Secretary-Treasurer.

The Alabama Chapter of the American College of Chest Physicians has elected: Dr. Norman Van Wezel, Foley, President; Dr. Arthur A. Calix, Decatur, Vice-President; and Dr. Charles R. Kessler, Birmingham, Secretary-Treasurer.

Officers of the Alabama Association of Obstetricians and Gynecologists are Dr. David B. Partlow, Tuscaloosa, President; Dr. Julian P. Hardy, Birmingham, Vice-President; and Dr. Joe F. Garner, Dothan, Secretary-Treasurer.

ARKANSAS

The Chicot County Medical Society has elected the following officers: Dr. V. H. Marques, Lake Village, President; Dr. A. G. Talbot, Lake Village, Secretary-Treasurer; and Dr. Major Smith, Dermott, Representative to the House of Delegates of the State Medical Convention.

New members of various county medical societies are *Baxter:* Dr. Arthur L. Beard, Gainesville, and Dr. Maxwell G. Cheney, Mountain Home; *Polk:* Dr. Calvin D. Austin, Mena; *Faulkner:* Dr. Bob G. Banister; *Franklin:* Dr. Evelyn R. Jones; *Pulaski:* Drs. Lee A. Martin and James Kelly Cornett, both of Little Rock; *Chicot:* Dr. Thomas C. Wilson, Dermott; *Cleburne:* Dr. W. M. Wells, Heber Springs; *Arkansas:* Dr. Nancy Kate Clary, Stuttgart; *Washington:* Dr. Joe C. Parker, Springdale; *Sebastian:* Drs. Archie L. Hewett and Eldon D. Pence, both of Fort Smith; *Boone:* Dr. Wilson E. Roark, Yellville; *Mississippi:* Drs. C. E. Holcomb and Edward L. Taylor, both of Blytheville; and *Conway:* Dr. Benjamin C. Hyatt, Perryville.

Dr. Ralph Weddington, Fayetteville, has been appointed Medical Director of Washington County.

Dr. John Grayden Cullins has been named Psychiatrist at the Benton Unit of the Arkansas State Hospital in Benton.

Dr. Thomas Moore Fletcher has been appointed Assistant Professor of Surgery, Division of Neurosurgery, at the University of Arkansas Medical Center in Little Rock. He is also on the staff of the Veterans Administration Hospital there.

Dr. Howard J. Barnhard, Little Rock, is First Vice-President of The Society of Nuclear Medicine, Southwestern Chapter.

DISTRICT OF COLUMBIA

Officers of the Washington Psychiatric Society are: Dr. Hewitt Varney, President; Dr. Sidney Berman, President-Elect; Dr. Leon Yochelson, Secretary; and Dr. Morris Kleinerman, Treasurer.

Dr. Martin M. Cummings, Chairman of the Department and Professor of Microbiology of the University of Oklahoma School of Medicine, has been selected to head the new Office of International Research at the National Institutes of Health.

Dr. Maurice H. Friedman is a newly-elected Trustee of the Equitable Life Insurance Company of Washington.

Recently certified by the American Board of Obstetrics and Gynecology were these Washington physi-

cians: Drs. James L. Breen, William F. Colliton, Jr., Ernest W. Lowe, Earl D. Neslen, Melvin W. Sandmeyer, Jr., George E. Stevens, and Charles E. Townsend.

FLORIDA

Officers of the Columbia County Medical Society are Dr. Harry S. Howell, President; Dr. Louis G. Landrum, Vice-President; and Dr. Thomas H. Bates, Secretary-Treasurer, all of Lake City.

Dr. Sidney Stillman has been installed as President of the Duval County Medical Society. Dr. Thomas M. Irwin is President-Elect; Dr. Archibald F. Caraway, Jr., Vice-President; Dr. Robert J. Brown, Secretary; and Dr. Lee S. Bransford, Jr., Treasurer. All are of Jacksonville.

The Escambia County Medical Society has these officers: Dr. P. G. Batson, Jr., President; Dr. Joseph L. Rubel, President-Elect; Dr. William T. Patton, Vice-President; and Dr. Vernon L. Smith, Secretary-Treasurer, all of Pensacola.

Dr. George A. Small, Assistant Director of the Department of Anesthesiology of St. Francis Hospital in Miami Beach, has been certified as a Diplomate of the American Board of Anesthesiology.

Dr. Sylvan A. Schotz, Miami, has been certified by the American Board of Internal Medicine.

Dr. J. Maxey Dell, Jr., Gainesville, has been elected to a 4 year term on the Board of Chancellors, the governing body of the American College of Radiology.

Dr. Melvin M. Simmons, Sarasota, has accepted appointment as a member of The National Foundation's Health Scholarship Committee for Florida.

New active members of the Florida Medical Association are: Dr. Russell P. Blanton, Cross City; Dr. I. Graydon Cloud, Lakeland; Dr. Gilbert M. Echelman, Tampa; Dr. Joseph H. Jackson, Jr., Palatka; Dr. Neils B. Jorgensen, Jr., Cocoa; Dr. James R. Kennedy, St. Augustine; Dr. Barney E. McRae, Jr., Lake City; Dr. John G. Madry, Jr., Melbourne; Dr. Robert C. Palmer, Jr., Pensacola; Dr. James M. Sinnett, Plant City; and Dr. Mark F. Wynn, Marathon.

Dr. Hawley H. Seiler, Tampa, was recently elected President of the Florida Tuberculosis and Health Association.

Dr. Melvin Levinson, Miami, has been certified by the American Board of Surgery.

Dr. Franklin J. Evans has won a two year term on the Coral Gables City Commission.

GEORGIA

Dr. J. H. Pinholster is Chief of Staff of Memorial Hospital in Savannah. Other officers are: Dr. J. L. Alexander, Vice-President; and Dr. J. Moultrie Lee, Secretary-Treasurer. The physicians are all of Savannah.

Officers of the Tift County Hospital medical staff are Dr. Charles Zimmerman, President; Dr. Tom L. Edmondson, Vice-President; and Dr. Henry K. Jarrett, Jr., Secretary-Treasurer, all of Tifton.

The medical staff of Memorial Hospital in Bainbridge has elected officers: Dr. E. Ashby Woods, Chief of Staff; Dr. Frank L. Gibson, Vice-Chief of Staff; and Dr. J. Walter Smith, Secretary, all of Bainbridge.

The new Chief of Staff at Houston County Hospital is Dr. William G. Talbert, Jr., Warner Robins.

New officers of Blue Shield, elected as the Georgia Physicians Service held its annual meeting recently, are Dr. H. Hilt Hammett, Jr., LaGrange, President; Dr. Luther H. Wolff, Columbus, Vice-President; and Dr. George P. Schuessler, Columbus, Secretary.

Dr. J. P. Woodhall is Chief of Staff at the Macon Hospital. Dr. John P. Jones is Vice-Chief of Staff, and Dr. Oscar S. Spivey is Secretary. The physicians are all of Macon.

As the newly-elected President of the Washington County Medical Society, Dr. William S. Helton, Sandersville, has also been named President of the Memorial Hospital in Sandersville. Also on the hospital staff will be Dr. Marion W. Hurt, Vice-President, and Dr. Joseph E. Lever, Secretary, both of Sandersville.

Dr. William E. Pound, Macon, has been elected Chairman of the Macon-Bibb County Board of Health.

Dr. Charles K. Richards, Calhoun, has assumed duties as Chief of the Gordon County Hospital medical staff. Dr. Byron A. Steele, Fairmount, is Vice-Chief of Staff.

Officers of the medical staff of John L. Hutcheson Memorial Tri-County Hospital, Fort Oglethorpe, are: Dr. Roy Pope, Jr., Chickamauga, Chief of Staff; Dr. T. W. Alsobrook, Rossville, Assistant Chief of Staff; and Dr. Robert T. Jones, Lafayette, Secretary.

New appointments at Emory University School of Medicine include Dr. Katharine Dodd, Professor of Pediatrics; Dr. Clarence A. Smith, Clinical Professor of Preventive Medicine and Community Health, part-time; and Dr. Marian F. Olansky, Instructor in Pediatrics, part-time. Dr. Earl Rasmussen has been promoted from Associate in Surgery to Assistant Professor of Surgery, part-time.

KENTUCKY

Dr. Carroll L. Witten, Louisville, Associate Councilor from Kentucky to the Southern Medical Association, has been re-elected Speaker of the Congress of Delegates of the American Academy of General Practice.

Dr. Gradie R. Rowntree, Louisville, is President of the Industrial Medical Association.

Officers of the Kentucky Industrial Medical Association include: Dr. Charles F. Martin, Lexington, President; Dr. Charles E. Allen, Jr., Louisville, President-Elect; Dr. Frederick P. Shepherd, Louisville, Vice-President; and Dr. Donald B. Thurber, Louisville, Secretary-Treasurer.

Dr. Edward H. Ray, Lexington, is President of the Kentucky Chapter of the American College of Surgeons. Dr. Laurence M. Quill, Newport, is Vice-President; and Dr. Richard F. Grise, Bowling Green, is Councilor.

New members of the Kentucky State Medical Association are: Drs. Carl J. Brueggemann, Clare C. Hugan, Jr., Douglas W. McKay, and Richard J. Menke, all of Covington; Drs. John L. Jenkins, Sheldon Kessler, and M. G. Veal, Jr., Henderson; Dr. William J. Beckmeyer, Ft. Thomas; Dr. John C. Davenport, Paris; and Drs. Robert G. Draime and Roger Haas, both of Newport.

LOUISIANA

The twenty-fifth annual meeting of The New Orleans Graduate Medical Assembly will be held March 12-15, 1962, with headquarters at The Roosevelt Hotel. Current officers are: Dr. Barrett Kennedy, President; Dr. Ralph M. Hartwell, President-Elect; Dr. W. E. Kittredge, First Vice-President; Dr. John G. Menville, Second Vice-President; Dr. H. Reichard Kahle, Third Vice-President; Dr. Mannie D. Paine, Jr., Secretary; and Dr. Samuel R. Staggers, Treasurer. The physicians are all of New Orleans.

MARYLAND

Dr. Nicholson J. Eastman, Baltimore, is President of the American College of Obstetricians and Gynecologists.

The following Maryland physicians have recently been certified by the American Board of Obstetrics and Gynecology: Dr. Pasquale De Felice, District Heights; Drs. Lional A. Desbordes, John D. Dumler, John H. Hebb, Erwin N. Hecker, Claude D. Hill, Joseph A. Knell, Jr., Richard F. Mattingly, Richard S. Munford, and George E. Wells, Jr., all of Baltimore; Dr. Leslie L. Mould, Cumberland; and Dr. Irwin W. Rovner, Takoma Park.

MISSISSIPPI

Dr. Lucian M. Ferris, Vicksburg, is President-Elect of the Mississippi Heart Association and Dr. Raymond F. Grenfell, Jackson, is Secretary.

Dr. John Vardaman Cockrell, Veterans Administration Center in Jackson, recently received the LL.B. degree.

Dr. Curtis P. Artz, Jackson, Associate Professor of Surgery at the University of Mississippi School of Medicine, is First Vice-President of the Southeastern Surgical Congress.

During the 93rd Annual Session of the Mississippi State Medical Association, Southern Medical Association had a breakfast honoring past and present officers and friends of SMA. This breakfast was held on May 11 in the Sun Room of the Buena Vista Hotel in Biloxi. Pictured above are, left to right, Mrs. James T. Thompson, Moss Point, Mississippi, General Chairman for the Annual Session of the Woman's Auxiliary to the Mississippi State Medical Association, and Chairman of the Committee on Resolutions for the Woman's Auxiliary to SMA; Dr. Leonard W. Larson, Bismarck, North Dakota, President-Elect of the American Medical Association; Mrs. Roy A. Douglass, Huntingdon, Tennessee, President-Elect of the Woman's Auxiliary to SMA; Dr. Guy T. Vise, Meridian, Councilor from Mississippi to SMA; Dr. Edwin H. Lawson, New Orleans, Past President of SMA; and Dr. George Lull, Chicago.

Dr. O. B. Crocker, Bruce, has been named to the Bruce School Board for a 5 year term.

Dr. M. V. Dardin, Vicksburg, is President of the Vicksburg Civitan Club.

President of the Bay Springs Rotary Club is Dr. W. R. Eure, Bay Springs.

Dr. J. A. Graves, Biloxi, has been elected to his fourth consecutive term as President of the School Board.

Dr. Guy Jarratt, Vicksburg, has been named a Director of the Vicksburg Rotary Club.

Dr. Edward Pennington, Ackerman, is President of the North Central Medical Society. Dr. Robert B. Townes, Grenada, is Secretary.

MISSOURI

Dr. Donald M. Dowell, Chillicothe, has been chosen President-Elect of the Missouri State Medical Association by the House of Delegates.

Officers of a 50 Year Club of members of the Missouri State Medical Association include Dr. Helmuth H. Kramolowsky, St. Louis, President; and Dr. C. L. Lawless, Marshall, Secretary.

Dr. Robert L. Magee, Eldorado Springs, has been honored as an outstanding young Missourian by the Missouri Junior Chamber of Commerce.

A recently elected Director of the Kansas City Rehabilitation Institute is Dr. Robert H. Fitzgerald, Independence.

The following Kansas City physicians are officers of the medical staff of the Children's Mercy Hospital in Kansas City: Dr. John H. Mayer, President; Dr. C. Y. Thomas, Vice-President; and Dr. C. Laurence Johnson, Secretary.

Officers of the Jasper County Medical Society are: Dr. John W. Koehler, Joplin, President; Dr. G. A. Schulte, Joplin, President-Elect; Dr. M. Foster Whitten, Carthage, Vice-President; Dr. D. O. Allen, Joplin, Secretary; and Dr. O. T. Blanke, Joplin, Treasurer.

New members of various medical societies in Missouri are: *Callaway County*, Drs. Henry A. Sydow and Edward R. Tellez, Fulton; *Audrain County*, Dr. Gordon Shaw, Mexico; *Jackson County*, Dr. James B. Seeley, Blue Springs; *Pemiscot County*, Dr. James C. Strittmatter, Caruthersville; *St. Louis County*, Drs. Edwin E. Carter and Frederick D. Peterson, St. Louis; and *St. Louis*, Dr. Charles W. Griege, Florissant; and Drs. Robert L. Bolton, G. Robert Bowles, Clarence L. Clark, John J. Lang, Lawrence N. McCullough, Nathan M. Simon, and Donald B. Stominger, all of St. Louis.

The following St. Louis physicians are officers of the medical staff of Jewish Hospital in St. Louis: Dr. M. Norman Orgel, President; Dr. Morris Abrams, Vice-President; Dr. Robert Karsh, Secretary; and Dr. Robert Burstein, Treasurer. Dr. Mary McFayden Bishop, St. Louis, has been appointed Assistant Clinical Director of the Department of Adult Psychiatry at the same hospital.

Dr. William Y. Eubank, Kansas City, was recently certified a Diplomate of the American Board of Internal Medicine.

Dr. Dean F. Werner, North Kansas City, is Vice-

Continued on page 44

Oklahomian is SMA's 178th Life Member

Dr. Joseph W. Kelso, Oklahoma City, recently became the 178th Life Member of Southern Medical Association. An active supporter of the Section on Gynecology, he has attended 15 of the annual meetings since he became a member of SMA in April 1938. Dr. Kelso and an associate, Dr. Joseph W. Funnell, placed First in the awards for Scientific Exhibits with their exhibit "Management of Gynecologic-Urologic Complications" at the 54th Annual Meeting in St. Louis last November. Mrs. Kelso, too, supports Southern Medical by active participation in its Woman's Auxiliary, having served as its President in 1948-49.

Life Membership in SMA offers a physician many advantages: You are able to pay your dues at one time, thereby preventing loss of membership or insurance coverage through oversight, future hardship, or disability. The full amount is deductible for Federal Income Tax purposes and you enjoy all the rights and privileges of active members. You will receive the *Southern Medical Journal* and other publications for life, and also a handsome permaplaque certificate, which requires no framing.

Physicians now on the Life Membership roster include:

Dr. R. E. Abell, Jr., Mobile, Alabama
Dr. Frank M. Acree, Greenville, Mississippi
Dr. C. Brown Alexander, San Antonio, Texas
Dr. Rufus H. Alldredge, New Orleans, Louisiana
Dr. W. H. Anderson, Booneville, Mississippi
Dr. John J. Andujor, Fort Worth, Texas
Dr. Daniel H. Autry, Little Rock, Arkansas
Dr. W. J. Barge, Miami, Florida
Dr. T. Neill Barnett, Richmond, Virginia
Dr. William Compere Basom, El Paso, Texas
Dr. Mylnor W. Beach, Charleston, South Carolina
Dr. James A. Becton, Birmingham, Alabama
Dr. Marion D. Bell, Dallas, Texas
Dr. Jacob Travis Bennett, El Paso, Texas
Dr. F. Lee Bivings, Atlanta, Georgia
Dr. Arthur P. Black, El Paso, Texas
Dr. John B. Black, Jacksonville, Florida
Dr. Joseph B. Bogan, Washington, D. C.
Dr. Harold H. Borders, St. Petersburg, Florida
Dr. Thomas C. Bost, Charlotte, North Carolina
Dr. George S. Bozalis, Oklahoma City, Oklahoma
Dr. H. B. Bradford, Cartersville, Georgia
Dr. Fred E. Brammer, Dania, Florida
Dr. John W. Brittingham, Augusta, Georgia
Dr. Leon Bromberg, Galveston, Texas
Dr. John F. Brownsberger, Washington, D. C.
Dr. James W. Brooks, Richmond, Virginia

Dr. Joseph W. Kelso, right, Oklahoma City, receives his SMA Life Membership plaque from Dr. Vernon D. Cushing, left, Councilor from Oklahoma to SMA, during the recent meeting of the Oklahoma State Medical Association.

Dr. E. V. Caldwell, Huntsville, Alabama
Dr. Fernando Carlomagno, New Orleans, Louisiana
Dr. Hjalmar E. Carlson, Kansas City, Missouri
Dr. Augustin S. Carswell, Augusta, Georgia
Dr. C. Whitney Caulkins, Jr., Waynesboro, Virginia
Dr. John S. Cayce, Nashville, Tennessee
Dr. Harry Lee Claud, Washington, D. C.
Dr. Cleveland D. Cochrane, Daytona Beach, Florida
Dr. O. S. Cofer, Atlanta, Georgia
Dr. K. W. Constantine (deceased April 1961), Palm Beach, Florida
Dr. David M. Cox, Louisville, Kentucky
Dr. Vernon D. Cushing, Oklahoma City, Oklahoma
Dr. Donald S. Daniel, Richmond, Virginia
Dr. Ross P. Daniel, Beckley, West Virginia
Dr. A. J. Davidson, Prestonburg, Kentucky
Dr. John W. Davis, Hickory, North Carolina
Dr. Nora D. Dean, Louisville, Kentucky
Dr. Charles H. Dickens, Madison, Georgia
Dr. Donald Thayer Dodge, San Antonio, Texas
Dr. W. LeRoy Dunn, Arlington, Virginia
Dr. Armando Duran, Lubbock, Texas
Dr. Lucien Y. Dyrenforth, Jacksonville, Florida
Dr. Thomas S. Edwards, Jacksonville, Florida
Dr. Robert E. Ellis, Oklahoma City, Oklahoma
Dr. H. B. Everett, Memphis, Tennessee
Dr. James R. Fancher, Chattanooga, Tennessee
Dr. Richard S. Flatt, Sarasota, Florida
Dr. M. Jay Flipse, Miami, Florida
Dr. Frank Leslie Fort, Jacksonville, Florida
Dr. Marvin L. Fowler, West Plains, Missouri
Dr. R. B. C. Franklin, Mount Airy, North Carolina
Dr. Leon Freedman, Baltimore, Maryland
Dr. Ellen D. Furey, Beaumont, Texas
Dr. Ellis F. Gates, Eagle Pass, Texas

Dr. J. F. Gipson, Ft. Stockton, Texas
Dr. George A. Glenn, Lexington, Kentucky
Dr. A. Gordon Goodall, Birmingham, Alabama
Dr. LeRoy Goodman, Yukon, Oklahoma
Dr. G. A. Guerra, Edinburg, Texas
Dr. C. E. Hamilton, Lafayette, Louisiana
Dr. Rudolph Hampton Hand, Anderson, South Carolina
Dr. C. R. Hedrick, Lenoir, North Carolina
Dr. William P. Herbst, Washington, D. C.
Dr. Edward R. Hipp, Sr., Charlotte, North Carolina
Dr. F. William Hoehn, Waco, Texas
Dr. Randolph H. Hoge, Richmond, Virginia
Dr. Kalford W. Howard, Portsmouth, Virginia
Dr. Harold H. Howell, Madison, West Virginia
Dr. Dick H. Huff, Oklahoma City, Oklahoma
Dr. Oscar B. Hunter, Jr., Washington, D. C.
Dr. Carl C. Irick, Webster Groves, Missouri
Dr. James R. Jeffrey, Battle Creek, Michigan
Dr. Jay J. Johns, Taylor, Texas
Dr. Ellsworth Johnson, Winchester, Virginia
Dr. Hollis E. Johnson, Nashville, Tennessee
Dr. Ray Hays Johnson, Louisville, Kentucky
Dr. W. O. Johnson (deceased Feb. 6, 1961), Louisville, Kentucky
Dr. Garland F. Jones, Jackson, Tennessee
Dr. H. Quillian Jones, Ft. Myers, Florida
Dr. Philip H. Jones, New Orleans, Louisiana
Dr. T. H. Jones, Waldo, Arkansas
Dr. Walter C. Jones, Miami, Florida
Dr. Helen Gladys Kain, Washington, D. C.
Dr. Samuel Elihu Kaplan, Venice, Florida
Dr. Maurice Kaufman, Lexington, Kentucky
Dr. H. L. Kearney, New Orleans, Louisiana
Dr. R. L. Kelly, Louisville, Kentucky
Dr. Joseph W. Kelso, Oklahoma City, Oklahoma
Dr. O. G. Kendrick, Tallahassee, Florida
Dr. Spencer A. Kirkland (deceased Dec. 29, 1960), Atlanta, Georgia
Dr. W. Merritt Kitcham, Kansas City, Missouri
Dr. Frederick Robert Klenner, Reidsville, North Carolina
Dr. W. Harding Kneedler, Davidson, North Carolina
Dr. Arthur M. Knight, Waycross, Georgia
Dr. Guy Edmond Knolle, Houston, Texas
Dr. Don S. Knowlton, Washington, D. C.
Dr. Amos R. Kootz, Baltimore, Maryland
Dr. Ambrose M. Langa, Columbia, Tennessee
Dr. Raymond E. Lenhard, Baltimore, Maryland
Dr. M. D. Levy, Houston, Texas
Dr. C. K. Linder, Columbia, South Carolina
Dr. A. H. Lisenby, Panama City, Florida
Dr. F. W. H. Logan, Rutherfordton, North Carolina
Dr. Mason I. Lowance, Atlanta, Georgia
Dr. Kenneth M. Lynch, Charleston, South Carolina
Dr. Alfonso F. Massaro, Tampa, Florida
Dr. Hugh W. Maxey, Jefferson City, Missouri
Dr. Lemuel E. Mayo, Portsmouth, Virginia
Dr. A. Clayton McCarty, Louisville, Kentucky
Dr. Robert H. McDonald, Newnan, Georgia
Dr. J. Calhoun McDougall, Atlanta, Georgia
Dr. John Phillip McGovern, Houston, Texas
Dr. Preston A. McLendon, Washington, D. C.
Dr. James C. Metts, Sr., Savannah, Georgia
Dr. J. Ethel Montgomery, Dania, Florida
Dr. Ramsay H. Moore, Dallas, Texas
Dr. Monte Leroy Moorer, Mobile, Alabama
Dr. Robert Dulaney Moreton, Ft. Worth, Texas
Dr. Carlisle Morse, Louisville, Kentucky
Dr. L. Thomas Morton, Charleston, North Carolina
Dr. James M. Moss, Alexandria, Virginia
Dr. Robert Edward Musgrave, Danville, Virginia
Dr. Luther Byron Newman, Oteen, North Carolina
Dr. Margaret M. Nicholson, Washington, D. C.
Dr. C. W. Norwood, Corinth, Mississippi
Dr. George W. Owen, Jackson, Mississippi
Dr. John M. Parato, St. Louis, Missouri
Dr. Boyd Hawthorne Payne, Staunton, Virginia
Dr. Jarrell Penn, Knoxville, Tennessee
Dr. J. M. Perret, New Orleans, Louisiana
Dr. W. H. Potts, Dallas, Texas
Dr. Gilbert A. Ratcliff, Huntington, West Virginia
Dr. Fount Richardson, Fayetteville, Arkansas
Dr. George E. Riley, Jackson, Mississippi
Dr. L. M. Riordan, St. Louis, Missouri
Dr. Harry E. Rollings, Savannah, Georgia
Dr. Carl J. Roncaglione, Charleston, West Virginia
Dr. Curtice Rosser, Dallas, Texas
Dr. W. J. Rosser, Birmingham, Alabama
Dr. Milford O. Rouse, Dallas, Texas
Dr. John F. Rowland (deceased October 1960), Hot Springs, Arkansas
Dr. Joe C. Rude, Austin, Texas
Dr. David A. Russell, Jr., Atlanta, Georgia
Dr. Charles B. Sanders, Houston, Texas
Dr. W. Y. Sayad, West Palm Beach, Florida
Dr. J. E. Schiffmacher, Kansas City, Missouri
Dr. William A. K. Seale, Sulphur, Louisiana
Dr. Harvey B. Searcy, Tuscaloosa, Alabama
Dr. Walter S. Sewell, Springfield, Missouri
Dr. J. S. Skaggs, Knoxville, Tennessee
Dr. David Sloane, West Palm Beach, Florida
Dr. Euclid M. Smith, Hot Springs, Arkansas
Dr. Howard O. Smith, Marlin, Texas
Dr. Alfred Sorensen, El Paso, Texas
Dr. A. L. Stabler, Birmingham, Alabama
Dr. Henry E. Steadman, Atlanta, Georgia
Dr. G. B. Stezler, Pennington Gap, Virginia
Dr. Harry J. Stone, Ashland, Kentucky
Dr. Leslie J. Stubblefield, Huntland, Tennessee
Dr. James A. Thom III, Baton Rouge, Louisiana
Dr. C. R. Thomas, Lookout Mountain, Tennessee
Dr. Guy Tittle, Dallas, Texas
Dr. Lee F. Turlington, Birmingham, Alabama
Dr. Carrol C. Turner, Memphis, Tennessee
Dr. Henry H. Turner, Oklahoma City, Oklahoma
Dr. Walter E. Vest, Huntington, West Virginia
Dr. S. P. Wainright, Birmingham, Alabama
Dr. William Gordon Wallace, Beaumont, Texas
Dr. A. M. Washburn, Little Rock, Arkansas
Dr. C. N. Watts, Charleston, West Virginia
Dr. James L. Wells, Orangeburg, South Carolina
Dr. Joseph E. Wheeler, Alexandria, Virginia
Dr. J. B. White, Amarillo, Texas
Dr. Anderson F. Whitsitt, Chestertown, Maryland
Dr. Fuller B. Whitworth, Cumberland, Maryland
Dr. C. Merrill Whorton, Jacksonville, Florida
Dr. Frank L. Williman, Washington, D. C.
Dr. George L. Winn, Oklahoma City, Oklahoma
Dr. Ward Wylie, Mullins, West Virginia
Dr. Buck J. Wynne, Jr., Dallas, Texas
Dr. Corren Pinckney Youmans, Miami, Florida
Dr. Iva C. Youmans, Miami, Florida
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2 does not produce ataxia, stimulate the appetite or alter sexual function

3 no cumulative effects in long-term therapy

4 does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis

5 does not muddle the mind or affect normal behavior

Usual dosage: One or two 400 mg. tablets t.i.d.
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; bottles of 50. Also as MEPROTABS*—400 mg. *unmarked*, coated tablets; and in *sustained-release* capsules as MEPROSPAN®-400 and MEPROSPAN®-200 (containing respectively 400 mg. and 200 mg. meprobamate).
*TRADE-MARK

Miltown®
meprobamate (Wallace)

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when allergies separate a man from his work...

Florists may develop allergies to flowers, insecticides and Holland bulbs... housewives to dust and soap... farmers to pollens and molds. All types of allergies – occupational, seasonal or occasional reactions to foods and drugs – respond to Dimetane. With Dimetane most patients become symptom free *and* stay alert, and on the job, for Dimetane works ... with a significantly lower incidence[1-6] of the annoying side effects usually associated with antihistaminic therapy.

CONTINUOUS 10-12 HOUR ACTION

Dimetane® Extentabs

parabromdylamine [brompheniramine] maleate

reliably relieve the symptoms...seldom affect alertness

Supplied: DIMETANE Extentabs®—12 mg. • DIMETANE Tablets—4 mg. • DIMETANE Elixir—2 mg./5 cc.

Dosage: *Extentabs:* Adults—One Extentab q. 8-12 h. or twice daily. Children over 6—one Extentab q. 12 h. *Tablets:* Adults—One or two tablets three or four times daily. Children over 6—one tablet t.i.d. or q.i.d. Children 3-6—½ tablet t.i.d. *Elixir:* Adults—2-4 teaspoonfuls t.i.d. Children over 6—2 teaspoonfuls t.i.d. or q.i.d. Children 3-6—1 teaspoonful t.i.d. Children under 3—0.5 cc. (0.2 mg.) per pound of body weight per 24 hours.

Side Effects: DIMETANE is usually well tolerated. Occasional mild drowsiness may be encountered. If desired, this may be offset by small doses of methamphetamine. Until known that the patient does not become drowsy, he should be cautioned against engaging in mechanical operations which require alertness.

Contraindications: Sensitivity to antihistamines. *Also Available:* Dimetane-Ten Injectable (10 mg./cc.) or Dimetane-100 Injectable (100 mg./cc.)

References: 1. Lineback, M.: The Eye, Ear, Nose and Throat Monthly *39*:342 (April) 1960. 2. Fuchs, A. M. and Maurer, M. L.: New York J. Med. *59*:3060 (August 15) 1959. 3. Kreindler, L. *et al.:* Antibiotic Med. and Clin. Therapy *6*:28 (January) 1959. 4. Schiller, I. W. and Lowell, F. C.: New England J. Med. *261*:478 (September 3) 1959. 5. Edmonds, J. T.: The Laryngoscope *69*:1213 (September) 1959. 6. Horstman, H. A.: Am. Pract. & Digest Treat. *10*:96 (January) 1959.

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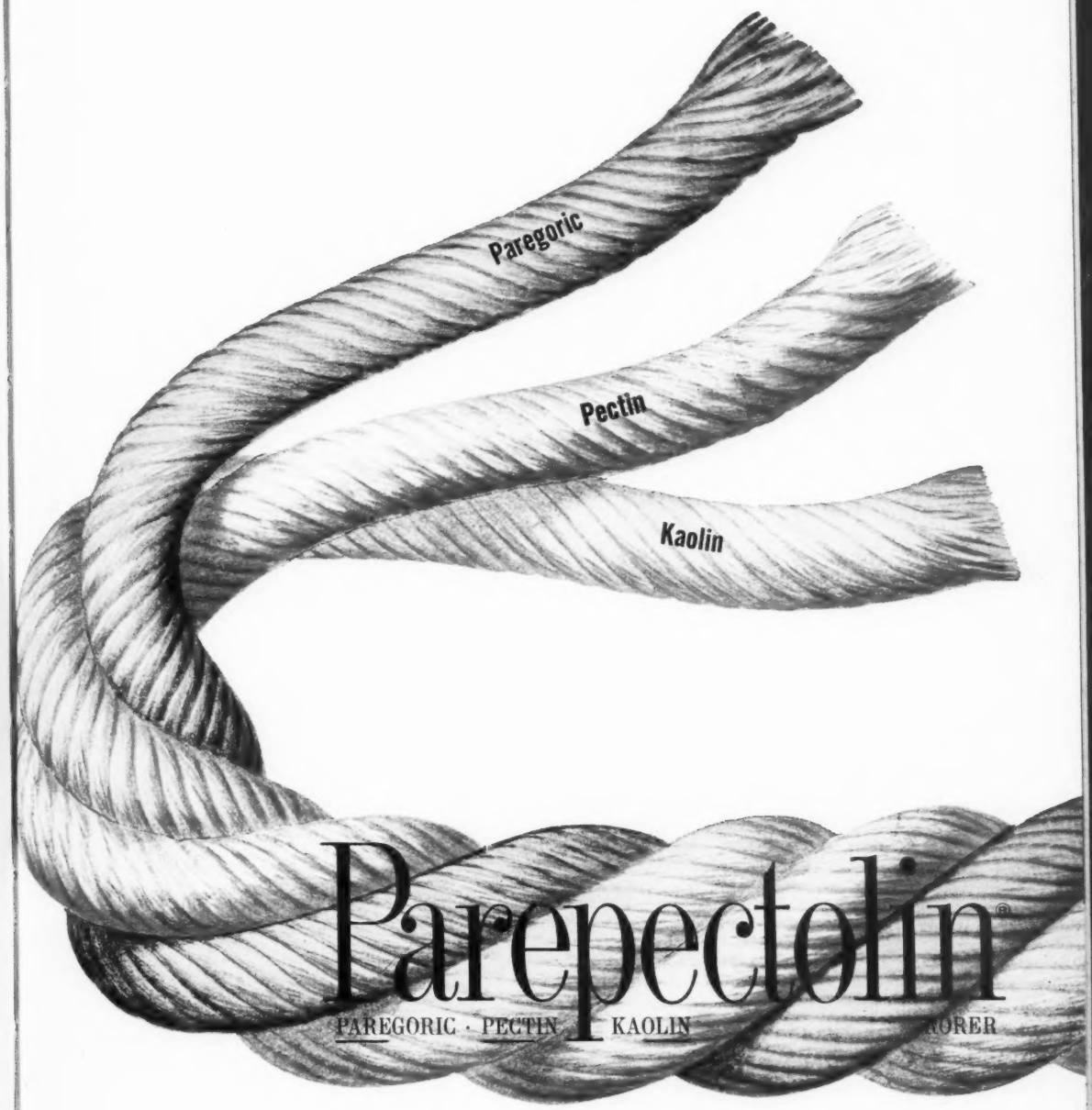

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Pleasant taste *plus* predictable, prompt response in diarrhea

Parepectolin combines paregoric, pectin, kaolin in *a balanced, stable colloidal suspension,* with a smooth, creamy consistency and a pleasant, mildly aromatic flavor. Parepectolin is compatible with antibiotics, and retains its uniform consistency and its good flavor.

Parepectolin; each fluid ounce—Paregoric (equivalent) 1.0 dram, Pectin 2.5 gr., Kaolin (specially purified) 85 gr. Bottles of 4 and 8 fluid ounces.

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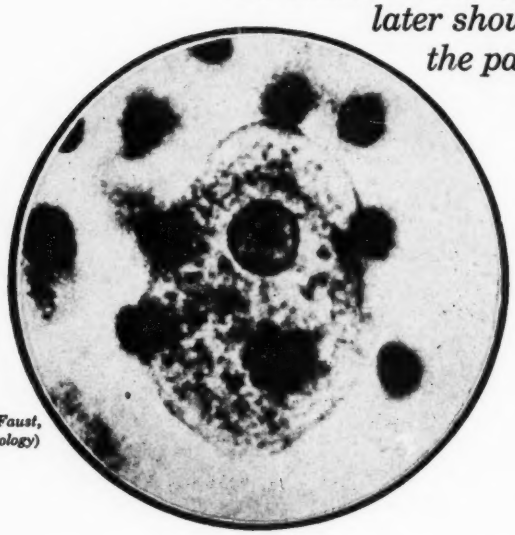
90% cures with ANAMEBA®

Re-examinations four months later showed 90% of the patients were still cured.



(From Craig and Faust, Clinical Parasitology)

19% INCIDENCE: ANAMEBA SPECIFIC FOR AMEBIASIS

Frye and Lampert[1] recently studied the effect of Anameba in the treatment of asymptomatic Endameba histolytica carriers. They concluded that "Results of treatment . . . with Anameba in a group of 23 carriers of E. histolytica were excellent. No toxic reactions or side effects were noted among the 49 subjects who received the drug . . . There was no nausea, diarrhea or other sign of toxicity or side effects."

RESULTS OF POST-TREATMENT STOOL EXAMINATIONS FOR E. HISTOLYTICA

No. of Patients Examined	No. of Controls	No. Positive Before Treatment	No. Positive After First Course of Treatment
135	26	23	2

8 DAYS OF TREATMENT RESULTS IN 90% CURES

A single course of treatment (1 tablet t.i.d. for 8 days) results in improvement or complete alleviation of symptoms. Relief of symptoms of abdominal distress and flatulence is prompt. No toxic reactions or side effects occur, and no alteration in diet is necessary during Anameba therapy.

Each Anameba tablet contains: Iodochlorhydroxyquin 125 mg., and Bacitracin-methylene disalicylate 5000 U.S.P. Units. *Supplied:* In bottles of 24 tablets.

When you suspect amebiasis—specify ANAMEBA. For additional information, please write our Medical Department.

1. Frye, W.W., and Lampert, R.: Treatment of Asymptomatic Endamoeba histolytica Carriers with a Formulation of Bacitracin-Methylene Disalicylate and Iodochlorhydroxyquin (Anameba). (To be published in Am. J. Gastroenterol., October, 1960.)

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bacterial
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Panalba*
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gain precious
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alba your broad-spectrum
antibiotic of first resort

In the presence of bacterial infection, taking a culture to determine bacterial identity and sensitivity is desirable—but not always practical in terms of the time and facilities available.

A rational clinical alternative is to launch therapy at once with Panalba, the antibiotic that provides the best odds for success.

Panalba is effective (in vitro) against 30 common pathogens, including the ubiquitous staph. Use of Panalba *from the outset* (even pending laboratory results) can gain precious hours of effective antibiotic treatment.

Supplied: Capsules, each containing Panmycin* Phosphate (tetracycline phosphate complex), equivalent to 250 mg. tetracycline hydrochloride, and 125 mg. Albamycin,* as novobiocin sodium, in bottles of 16 and 100.
Usual Adult Dosage: 1 or 2 capsules 3 or 4 times a day.
Side Effects: Panmycin Phosphate has a very low order of toxicity comparable to that of the other tetracyclines and is well tolerated clinically. Side reactions to therapeutic use in patients are infrequent and consist principally of mild nausea and abdominal cramps.
Albamycin also has a relatively low order of toxicity. In a certain few patients, a yellow pigment has been found in the plasma. This pigment, apparently, a metabolic by-product of the drug, is not necessarily associated with abnormal liver function tests or liver enlargement.
Urticaria and maculopapular dermatitis, a few cases of leukopenia and agranulocytosis have been reported in patients treated with Albamycin. Most of these side effects usually disappear upon discontinuance of the drug.
Caution: Since the use of any antibiotic may result in overgrowth of nonsusceptible organisms, constant observation of the patient is essential. If new infections appear during therapy, appropriate measures should be taken.
Total and differential blood counts should be made routinely during prolonged administration of Albamycin. The possibility of liver damage should be considered if a yellow pigment, a metabolic by-product of Albamycin, appears in the plasma. Panalba should be discontinued if allergic reactions that are not readily controlled by antihistaminic agents develop.

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in the wide middle region of pain

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Salts of Dihydrohydroxycodeinone and Homatropine, plus APC

TABLETS

fills the gap between mild oral and potent parenteral analgesics[1-7]

- **acts in 5-15 minutes**
- **relief usually lasts 6 hours or longer**
- **toleration excellent... constipation rare**
- **sleep uninterrupted by pain**

Each Percodan* Tablet contains 4.50 mg. dihydrohydroxycodeinone HCl, 0.38 mg. dihydrohydroxycodeinone terephthalate (warning: may be habit-forming), 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. acetophenetidin, and 32 mg. caffeine.

for fast and thorough pain relief

AVERAGE ADULT DOSE
1 tablet every 6 hours. May be habit-forming. Federal law permits oral prescription.

Also Available
For greater flexibility in dosage—Percodan®-Demi: The complete Percodan formula, but with only half the amount of salts of dihydrohydroxycodeinone and homatropine.

1. Blank, P., and Boas, H.: Improved analgesia for moderate pain. Ann. West. Med. & Surg. 6:376, 1952. 2. Bonica, J. J., et al.: The management of postpartum pain with dihydrohydroxycodeinone (Percodan): Evaluation with codeine and placebo. West. J. Surg. 65:84, 1957. 3. Cass, L. J., and Frederick, W. S.: A controlled study in pain relief. M. Times 84:1318, 1956. 4. Chasko, W. J.: Pain-free dental surgery: Postoperative extension of the pain-free state. J. District of Columbia Dent. Soc. 31:3, No. 5, 1956. 5. Cozen, L.: Office Orthopedics, ed. 2, Philadelphia, Lea & Febiger, 1953, pp. 120, 138, 145, 156, 234. 6. Nicolson, W. P., Jr., and Skandalakis, J. E.: Control of postoperative pain. J.M.A. Georgia 46:471, 1957. 7. Piper, C. E., and Nicklas, F. W.: Percodan for pain in industrial practice. Indust. Med. 23:510, 1954, abstracted, Clin. Med. 3:1008, 1956. Current M. Digest 22:135, No. 3, 1955.

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ORAL ALLERCUR REACHES THE SKIN IN 10 MINUTES[1] FOR PROLONGED RELIEF

Allercur is the systemic answer to a dermatology problem. This single agent provides fast, prolonged relief of itching, both allergic and nonallergic, with only 2 to 4 tablets daily —without timed-release devices. Drowsiness and other side effects are of low degree. Unlike topical preparations, Allercur frees the patient of messy, inconvenient local application. Many risks of systemic phenothiazine and glucocorticoid therapy are decreased.

Effective: "An excellent or good antipruritic response occurred in 69 patients (79.5%). No toxic reactions occurred and there were virtually no side effects. Particularly notable were the absence of drowsiness and the rapidity with which the remission of itching occurred."[2] Allercur is also effective in the management of conditions such as nasal allergy, including seasonal hay fever.

CAUTION: If drowsiness occurs, patients should avoid activities demanding alertness.

AVERAGE DOSE: 2 to 4 tablets daily in divided doses.

SUPPLIED: Tan, scored tablets, each containing 20 mg. clemizole HCl, in bottles of 100.

REFERENCES: 1. Kimmig, J.: Hautarzt 3:414 (Sept.) 1952. 2. Butler, P.G.: Western Med. 1:16 (Nov.) 1960. Bibliography on request.

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Science for the World's Well-Being®

when allergies occur Rx

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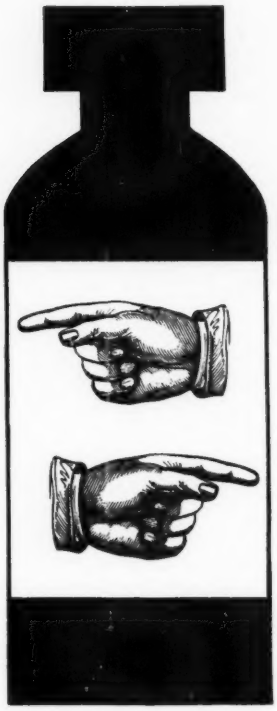
*Reg. T.M., Schering, A. G., Berlin

(clemizole HCl)

Trademarked drugs . . .



or "drugs anonymous"?

In the field of medicine, as almost everywhere else in a free economy, the trademark concept has evolved over the years. As with most human institutions, there are some who may not consider it ideal; but it has brought about three signal benefits:

To the physician it gives assurance of quality in the drugs he prescribes—assurance backed by the biggest asset of the maker, his reputation.

To the manufacturer it gives one of the greatest possible incentives to produce new and better curative agents.

To the pharmacist it gives preparations which he can dispense with confidence.

If trademarks are done away with, a whole new setup must be created:

1. An enormously expanded, expensive system of government quality control.

2. A new system of generic nomenclature which would magically turn out names not only rememberably simple, but also conforming to the principles of complex chemical terminology.

3. Something new to fill the gap left by the elimination of the trademark incentive to produce new and better drugs.

The American system has been pre-eminent in producing and distributing good medicines. Above all it has been successful in creating new advances in therapy. In a dubious effort to provide cheaper medicines by abolishing the trade names upon which the responsible makers stake their reputations, let us beware of sacrificing this success.

This message is brought to you on behalf of the producers of prescription drugs to help you answer your patients' questions on this current medical topic. For additional information, please write **Pharmaceutical Manufacturers Association, 1411 K Street, N. W., Washington 5, D.C.**

In skeletal muscle spasm

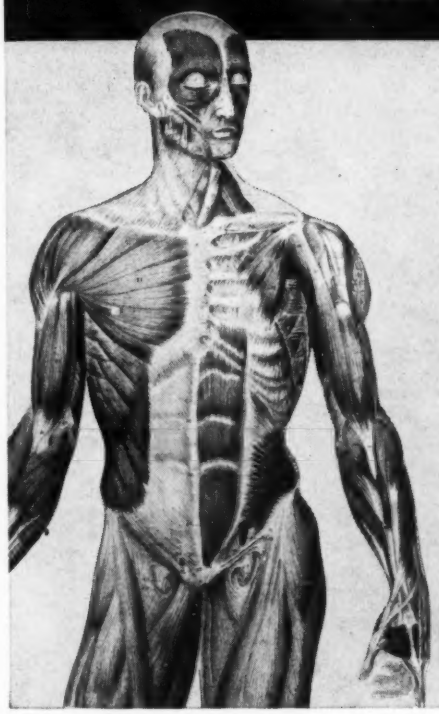
NORFLEX®*

orphenadrine citrate 100 mg. tablets

quickly resolves the spasm . . .

relieves the pain . . .

restores normal function



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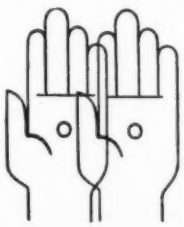
may last up to 12 hours after administration . . . permits uninterrupted sleep at night . . . does not interfere with daytime alertness . . . only the muscles in spasm respond . . . no lessening of general muscle tonus.

Contraindications:

Routine precautions against use of anticholinergic drugs should be observed. Norflex should be used with caution in glaucoma, tachycardia, or urinary retention.

Simple dosage



for all adults regardless of age or sex: 2 tablets daily—one in the morning, one in the evening—easily remembered . . . offers better patient cooperation.

NORFLEX is a product of

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in its completeness

Each pill is equivalent to one USP Digitalis Unit

Physiologically Standardized therefore always dependable.

Clinical samples sent to physicians upon request.

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Continued from page 822

President of the American Association of Railway Surgeons.

Dr. Louis Porter, Kansas City, has been elected President of the Kansas City Tufts Club.

Dr. Ralph K. Earp is President of the St. Louis Orthopedic Society. Other officers include: Dr. Vilray P. Blair, Jr., Vice-President; and Dr. George E. Scheer, Secretary-Treasurer. The physicians are all of St. Louis.

Officers of the Barnes and Allied Hospitals Society are: Dr. Michael M. Karl, President; Dr. Louis T. Byars, President-Elect; Dr. Edward Reinhard, Vice-President; and Dr. Ross B. Sommer, Secretary-Treasurer, all of St. Louis.

Dr. Frank McDowell, Associate Professor of Clinical Surgery at Washington University School of Medicine in St. Louis, was recently elected Vice-President of the American Association of Plastic Surgeons.

Recently certified by the American Board of Obstetrics and Gynecology were the following Missouri physicians: Drs. H. Marvin Camel, Justin F. Kraner, Marvin Rennard, and Clarence M. Turner, all of St. Louis; Drs. Walter F. Haith and Robert L. Hanes, both of Kansas City; Dr. David G. Hall, Columbia; Dr. Harry S. Jonas, Jr., Independence; Drs. Raymond O. Keltner and John A. Sheahon, both of Raytown; Dr. Fred E. Rawlins, Cape Girardeau; and Dr. Mitchell Yanow, Clayton.

NORTH CAROLINA

Dr. William P. Wilson has been appointed Associate Professor of Psychiatry and Head of the Psychiatry Department's Electroencephalography Division at Duke University School of Medicine in Durham. Dr. Joseph K. Isley has been appointed Associate Professor of Radiology and Medical Director of the Radioisotope Laboratory at Duke University Medical Center.

Dr. Kenneth M. Brinkhous, Chapel Hill, is Secretary-Treasurer of the American Society for Experimental Pathology.

Dr. Harold D. Green, Gordon Gray Professor of Physiology at Bowman Gray School of Medicine in Winston-Salem, has been named to the scientific council of the Institute for Advancement of Medical Communication.

New members of the Medical Society of the State of North Carolina are: Dr. Thomas E. Ross, Rockingham; Dr. George W. Galloway, Jr., Hamlet; Dr. Roy V. Berry, McCain; Dr. Harry L. Johnson, Jr., Granite Quarry; Dr. Bobby M. Foster, Mocksville; Dr. Robert B. McQueen, Graham; Drs. Robert Yudell and Jeanne M. Voltaggio Sing, both of Charlotte; and Drs. Donald B. Hackel and William P. Wilson, both of Durham.

The following North Carolina physicians have been certified by the American Board of Obstetricians and Gynecologists: Major Maurice S. Berbary, Ft. Bragg; Dr. Ben R. Boyette, Jr., Goldsboro; Dr. Clifford C. Byrum, Raleigh; Dr. Maurice G. Couturier, Sr., Reidsville; Drs. Posey E. Downs and Rufus P. Rankin, Jr., both of Charlotte; Drs. Amzi J. Ellington, Jr., and Charles L. Saunders, Jr., both of Burlington; Dr. Raymond C. Houghton, New Bern; Dr. Clayton J.

Continued on page 46

FOR PROVEN EFFICACY IN INFECTIOUS DIARRHEAS

Humatin® KAPSEALS

(paromomycin, Parke-Davis)

A WELL-TOLERATED ANTIBIOTIC-AMEBICIDE

HUMATIN possesses high antibacterial and antiamebic activities, coupled with a low order of oral toxicity.[1] Because it is effective against many gram-negative pathogens, HUMATIN has proved valuable in the treatment of infectious diarrheas and other enteric infections, most of which are caused by bacilli of the gram-negative group.[2-5] Characteristic of the favorable response to HUMATIN is a prompt reduction in the number of stools per day, a decrease in fever, and rapid alleviation of other symptoms of infection.[2,3,5] HUMATIN is also useful in all phases of intestinal amebiasis,[1,5-12] and has shown promise of being useful in the preoperative suppression of intestinal flora,[5] and in the adjunctive management of hepatic coma.[13-15]

HUMATIN is not appreciably absorbed from the gastrointestinal tract and is, therefore, not effective against systemic infections. Systemic toxicity has not been a problem. *See medical brochure for details of administration, precautions, and dosage.*

SUPPLIED: HUMATIN (paromomycin, Parke-Davis) is available as the sulfate in Kapseals,® each containing the equivalent of 250 mg. of base, in bottles of 16.

REFERENCES: (1) Coffey, G. L., *et al.: Antibiotics & Chemother.* 9:730, 1959. (2) Courtney, K. O.; Thompson, P. E.; Hodgkinson, R., & Fitzsimmons, J. R.: *Antibiotics Annual* 7:304, 1959-1960. (3) Godenne, G. D.: *ibid.*, 310. (4) McMath, W. F. T., & Hussain, K. K.: *Pub. Health* 73:328, 1959. (5) Personal Communications to Department of Clinical Investigation, Parke, Davis & Company, 1959. (6) Shafei, A. Z.: *Antibiotic Med. & Clin. Therapy* 6:275, 1959. (7) Lopez Elias, F., & Oliver-Gonzalez, J.: *Antibiotic Med. & Clin. Therapy* 6:584, 1959. (8) Carter, C. H.: *Antibiotic Med. & Clin. Therapy* 6:586, 1959. (9) Thompson, P. E., *et al.: Antibiotics & Chemother.* 9:618, 1959. (10) Dooner, H. P.: *Antibiotic Med. & Clin. Therapy* 7:486, 1960. (11) Coles, H. M. T., *et al.: Lancet* 1:944, 1960. (12) Moffett, H. F., & Toh, S. H.: *Antibiotic Med. & Clin. Therapy* 7:569, 1960. (13) Fast, B. B.; Wolfe, S. J.; Stormont, J. M., & Davidson, C. S.: *Arch. Int. Med.* 101:467, 1958. (14) Mackie, J. E.; Stormont, J. M.; Hollister, R. M., & Davidson, C. S.: *New England J. Med.* 259:1151, 1958. (15) Stormont, J. M.; Mackie, J. E., & Davidson, C. S.: *New England J. Med.* 259:1145, 1958.

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Continued from page 44

Jones, Concord; Dr. Talbot F. Parker, Jr., Goldsboro; and Dr. Bessie Kay Williams, High Point.

OKLAHOMA

Dr. Fred E. Woodson, a member of the faculty of the University of Oklahoma School of Medicine, has been initiated as a faculty member of Alpha Omega Alpha.

Recently certified by the American Board of Obstetrics and Gynecology were the following Oklahoma physicians: Drs. Sam W. Hendrix and George H. Jennings, both of Oklahoma City.

SOUTH CAROLINA

Officers of the Coastal Medical Society are: Dr. Ford Rivers, Charleston, President; Dr. Gus Richards, Charleston, Vice-President; and Dr. Warren S. Smith, Walterboro, Secretary-Treasurer.

Dr. John A. McLeod, Lockhart, is President of the Union County Medical Society.

Dr. Robert S. Solomon, Moncks Corner, is President of the Moncks Corner Chamber of Commerce, and Dr. P. E. Myers, also of Moncks Corner, is Vice-President.

Dr. Malcolm U. Dantzler, Chapel Hill, has been approved to succeed Dr. Leon Banov, Charleston, as Director of the Charleston Health Department.

Faculty news from the Medical College of South Carolina in Charleston includes the following appointments: Dr. Frederick E. Kredel, Professor of Clinical Surgery; Dr. R. Randolph Bradham, Acting Professor of Surgery; and Dr. R. W. Hanckel, full-time Professor of Otolaryngology.

Dr. C. Warren Irvine, Jr., Columbia, is Vice-President of the South Carolina Heart Association. Dr. Allen B Warren, Jr., Spartanburg, is Secretary.

Clemson College in Clemson has named Dr. George G. Durst, Sullivan's Island, President-Elect of its Alumni Association.

The American Board of Obstetrics and Gynecology has certified the following South Carolina physicians: Dr. Mary Elizabeth Blanchard, Sumter; Dr. William R. Griffin, Conway; Dr. John Dallas Bunch, Jr., Columbia; Dr. Louis E. Nesmith, Charleston; and Dr. Louis M. Palles, Florence.

TENNESSEE

Officers of the Tennessee State Medical Association are Dr. W. O. Vaughan, Nashville, President; and Dr. William J. Sheridan, Chattanooga, President-Elect.

Dr. John B. Steele, Chattanooga, has been chosen by the Tennessee State Medical Association as its Physician of the Year.

Dr. C. B. Roberts, Sparta, is President of the Upper Cumberland Mental Health Association.

Dr. Robert W. Noyes, Stanford University School of Medicine, has been appointed Professor and Head of the Department of Obstetrics and Gynecology at Vanderbilt University School of Medicine in Nashville.

Dr. Alfred D. Mason, Memphis, is President of the Southeastern Section of the American Urological Association.

Dr. McChesney Goodall, Knoxville, is a Director of the Knoxville Chamber of Commerce.

Continued on page 48

For the irritable G.I. tract

Milpath acts quickly to suppress hypermotility, hypersecretion, pain and spasm, and to allay anxiety and tension with minimal side effects.

AVAILABLE IN TWO POTENCIES

MILPATH-400—Yellow, scored tablets of 400 mg. Miltown (meprobamate) and 25 mg. tridihexethyl chloride.
Bottle of 50.

Dosage: 1 tablet t.i.d. at mealtime and 2 at bedtime.

MILPATH-200—Yellow, coated tablets of 200 mg. Miltown (meprobamate) and 25 mg. tridihexethyl chloride.
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Dosage: 1 or 2 tablets t.i.d. at mealtime and 2 at bedtime.

Milpath®

®Miltown + *anticholinergic*

WALLACE LABORATORIES *New Brunswick, N. J.*

Continued from page 46

Dr. Howell H. Sherrod, Johnson City, has been elected President of the Tennessee State Orthopedic Society. Other officers are Dr. Merritt B. Shobe, Kingsport, Vice-President; and Dr. Robert Strang, Kingsport, Secretary.

Dr. D. L. Brint, Bolivar, is the new President of the Rotary Club of Bolivar.

Dr. Alex Carabia, formerly of Huntington, West Virginia, has been appointed Pathologist and Director of Laboratories at the Oak Ridge Hospital.

Dr. Dillard Sholes, Elizabethton, has been elected President of the Carter County Unit of the American Cancer Society.

Dr. Bruce B. Bellomy, Knoxville, is Director of Pathology and Laboratories at Presbyterian Hospital.

Several Tennessee physicians have recently been certified by the American Board of Obstetrics and Gynecology: Drs. Albert May Alexander, Betty Jane Schettler, and Louie C. Henry, all of Memphis; Dr. James A. Langdon, Jackson; Dr. Norman A. McKinnon, Jr., Maryville; and Dr. Philip A. Nicholas, North Nashville.

TEXAS

Dr. James D. Murphy, Fort Worth, has been named President-Elect of the American Academy of General Practice.

The Texas Medical Association has the following new officers: Dr. Harvey Renger, Hallettsville, President; Dr. George Waldron, Houston, President-Elect; Dr. R. Mayo Tenery, Waxahachie, Vice-President; Dr. James D. Murphy, Fort Worth, Speaker of the House of Delegates; and Dr. Charles Max Cole, Dallas, Vice-Speaker of the House of Delegates.

Dr. Clark C. Campbell, Itasca, has been selected as the 1961 Practitioner of the Year by the Texas Medical Association.

Dr. Maurice C. Barnes, Waco, is Secretary of the American College of Allergists.

Dr. Dorothy Mainland Brown, Catarina, has been elected Secretary-Treasurer of the La Salle-Frio-Dimmitt County Medical Society.

Officers of the Panhandle (Third) District Medical Society are: Dr. Macfield McDaniel, Pampa, President; Dr. A. W. Bronwell, Lubbock, President-Elect; Dr. Dale Watkins, Wellington, First Vice-President; Dr. J. Victor Ellis, Amarillo, Second Vice-President; and Dr. H. Fred Johnson, Amarillo, Secretary.

The University of Texas Medical Branch in Galveston has announced the appointment of Dr. Alois Vasicka as Professor in the Obstetrics and Gynecology Department. Dr. Raymond L. Gregory, Professor of Medicine since 1942, has been named Chairman of the Department of Internal Medicine.

Dr. William J. Campbell, Amarillo, has been elected President of the Amarillo School Board. He is also a member of the Amarillo College Board of Regents.

Continued on page 50

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DEBITTERED
Genuine • Grain Grown
BREWERS' YEAST
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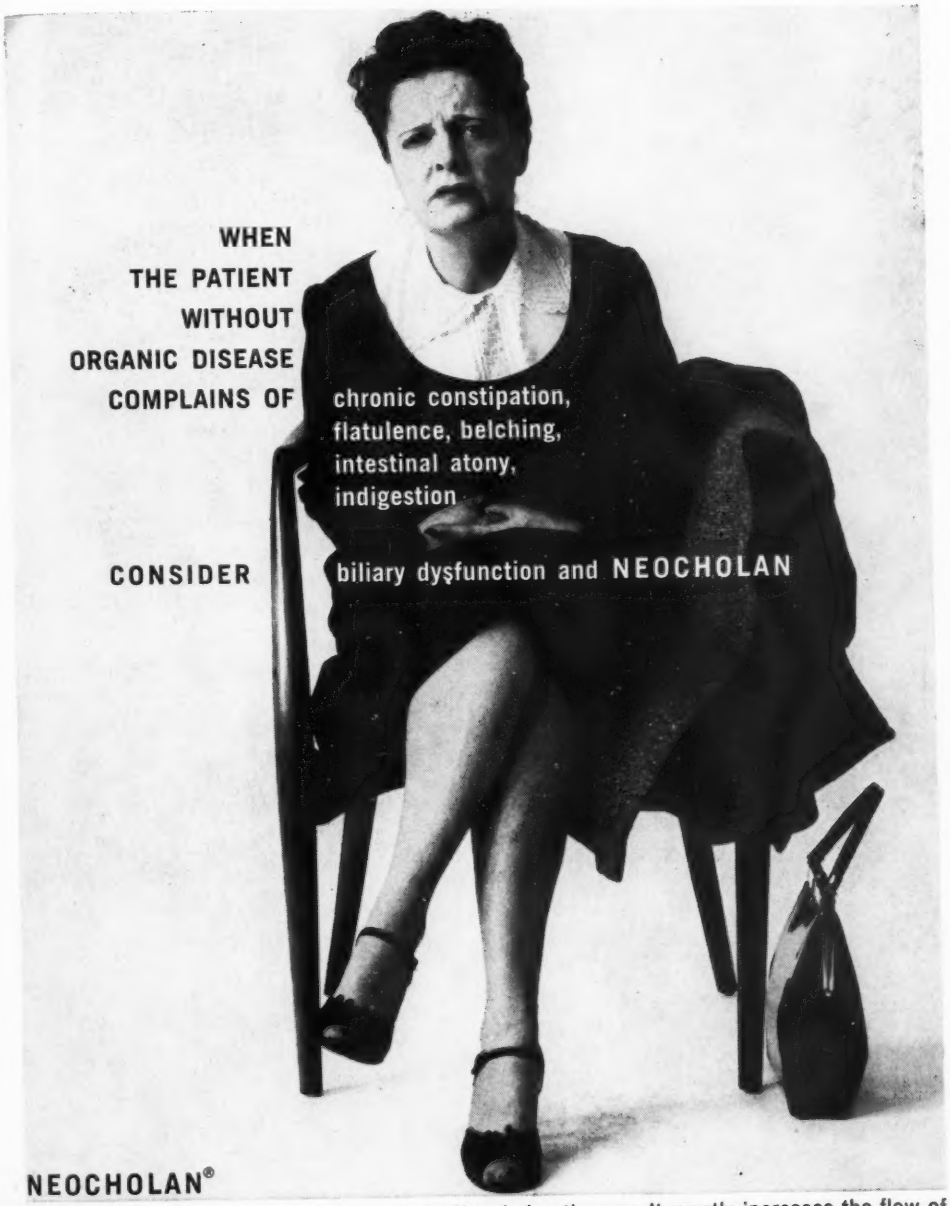

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Continued from page 48

Dr. E. F. Etter, Sherman, has been elected to the Board of Directors of the Grayson County State Bank.

Dr. J. Arnold Bargen, Temple, has been re-elected to membership on the Council on Scientific Assembly, American Medical Association.

Among officers of The Society of Nuclear Medicine, Southwestern Chapter, are Dr. Ruskin C. Norman, San Antonio, President-Elect; Dr. Donald A. Sutherland, Dallas, Second Vice-President; and Dr. J. R. Maxfield, Jr., Dallas, Secretary-Treasurer.

Dr. Edward B. Singleton, Houston, has been elected Surgeon General of the Texas Exes Association of the University of Texas.

The Corpus Christi Surgical Society's officers include: Dr. H. J. Eberle, President; Dr. R. R. Woods, Vice-President; Dr. M. C. Kendrick, Secretary; and Dr. G. B. Barnes, Treasurer, all of Corpus Christi.

Dr. Raleigh R. White, Temple, is Vice-President of Certified Investment Company, Inc.

Dr. Terrell Speed, Temple, was recently re-elected to the Board of the Temple Independent School District.

Dr. Walter G. Crowe has joined the staff of King's Daughters Clinic in Temple.

Dr. Olin B. Gober, President of the Scott and White Clinic in Temple, has been elected to the Board of Directors of the Blue Shield Plan.

Dr. Valiant C. Baird, Houston, has been appointed to the newly-created position of Medical Director in the headquarters organization of Humble Oil and Refining Company.

Drs. G. V. Brindley, Sr., T. F. Bunkley, J. S. McCelvey, and A. C. Broders, Sr., all of Temple, have been elected to honorary membership by the Bell County Medical Society.

Recently certified by the American Board of Obstetrics and Gynecology were the following Texas physicians: Drs. John D. Carson and Frank J. Lee, both of Wichita Falls; Drs. Leonard A. Charpentier and Leslie C. Powell, Jr., both of Galveston; Dr. Juan Garcia-Esteves, McAllen; Dr. Robert C. Koehn, Jr., Sheppard AFB; Dr. Maurice V. Korkmas; Irving; Dr. James R. Morgan, El Paso; Dr. Marion L. Stahl, Austin; Drs. Kent P. Upchurch and Allen G. Williams, both of Pasadena; Drs. Reuben H. Adams, Donald F. Fangman, and Richard A. Sparr, all of Dallas; and Drs. Joe Atlas, William J. Estrada, Alfred E. Lauden, and Orian C. Westbrook, all of Houston.

VIRGINIA

Officers of the Wise County Medical Society include Dr. Pierce Nelson, Norton, President; Drs. Donald Shelley, H. H. Howze, and C. I. Fuller, Vice-Presidents, all of Norton; and Dr. C. E. Swecker, Wise, Secretary-Treasurer.

Dr. W. C. Welburn, Arlington, has been named the first honorary Chief of Staff of the Arlington Hospital.

The Virginia Pediatric Society has the following officers: Dr. John T. Walke, Roanoke, President; Dr.

Continued on page 52

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Continued from page 50

Gayle G. Arnold, Richmond, Vice-President; and Dr. C. C. Powel, Harrisonburg, Secretary-Treasurer.

Dr. Paul Camp, Richmond, has been elected President of the Phi Beta Kappa Association of Richmond.

Dr. George Cooper, Jr., Charlottesville, has been elected Chairman of the Councilors of the American College of Radiology.

Dr. Thomas L. Gorsuch, Waynesboro, is President of the Waynesboro Rotary Club.

Continued on page 54

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Continued from page 52

Dr. John W. Emerick, Jr., Berryville, has been appointed Councilman of Ward No. 1 of Berryville.

The new Manager of McGuire VA Hospital in Richmond is Dr. Robert J. Scott.

The American Board of Obstetrics and Gynecology has recently certified the following Virginia physicians. Dr. Peter Bartsch, Richlands; Dr. Thomas P. Caine, Jr., Newport News; Drs. Frederick T. Given, Jr., William N. Reingold, and Gilbert F. Rieman, all of Norfolk; Dr. Philip S. Grant, Staunton; Dr. Luther J. Hamlett, Roanoke; Dr. Robert W. Irvin, Jr., Fort Eustis; Dr. Herbert C. Jones, Jr., Charlottesville; Dr. Charles B. Marshall, Martinsville; and Dr. Glenn B. Updike, Jr., Danville.

New members of the Medical Society of Virginia are: Dr. Robert Koth, Arlington; Drs. Audrey K. Brown, Antonio Rodriguez-Antunez, and John H. Vansant, all of Charlottesville; Dr. Ernesto V. Castro, Falls Church; Dr. Silvia Luik, Marion; Dr. Enrico Davoli, McLean; Dr. Constantine N. Psimas, Portsmouth; Drs. Raymond A. Adams, John A. Gill, Niall P. MacAllister, George R. Prout, Jr., and Robert A. Senescu, all of Richmond; Dr. Robert T. Hyde, Sr., Staunton; Dr. Jose A. de Lamerens, Suffolk; and Dr. Harry S. Brown, Vienna.

WEST VIRGINIA

The annual meeting of the West Virginia Heart Association will be held at the West Virginia University Medical Center, Morgantown, on Friday, Sept. 15, 1961, 9:00 a.m. to 5:00 p.m. The all-day program for physicians will be presented by the teaching staff of the West Virginia University Medical Center. For futher information contact the West Virginia Heart Association, 1906 Washington Street East, Charleston.

Dr. Albert C. Esposito, Huntingdon, Secretary of the Section on Ophthalmology and Otolaryngology for Southern Medical Association, is the new President of the West Virginia Academy of Ophthalmology and Otolaryngology. Other officers of the Academy include Dr. William K. Marple, Huntington, President-Elect; Dr. James T. Spencer, Charleston, Vice-President; and Dr. Worthy W. McKinney, Beckley, Secretary-Treasurer.

Dr. George Gevas, Parkersburg, has been inducted as a Fellow of the American College of Obstetricians and Gynecologists.

New members of the West Virginia State Medical Association are: Dr. Michael J. Caruso, Wheeling; Dr. Harry L. Craig, Whitesville; Dr. Charles R. Daniel, Drexel Hill, Pennsylvania; Dr. Richard O. Gale, Welch; Dr. Thomas K. Mahan, Beckley; and Dr. Richard L. Slack, Pt. Pleasant.

A husband and wife team has been appointed to the faculty at the West Virginia University School of Medicine. Dr. Wilhelm S. Albrink is Professor and Chairman of the Department of Pathology, and his wife, Dr. Margaret Albrink, is Associate Professor of Medicine.

Dr. Harvey S. Klein, Huntington, and Dr. Chester L. Wagstaff, Williamson, have both been certified by the American Board of Obstetrics and Gynecology.

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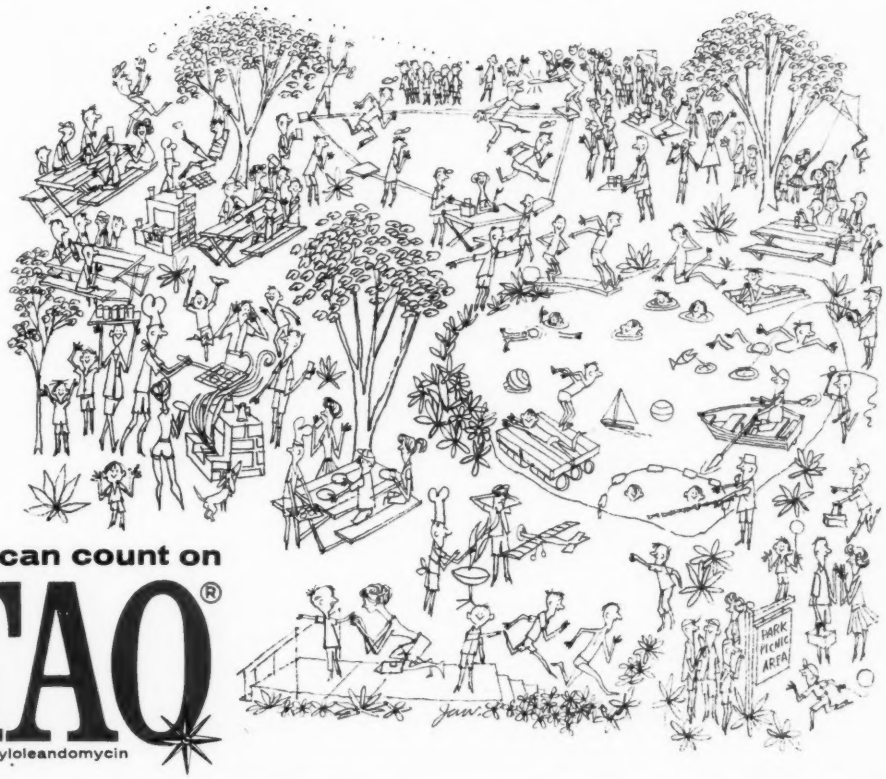

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References: 1. LeFebvre, M., et al.: Antibiotics Annual 1959-1960, New York, Antibiotica, Inc., 1960, p. 755. 2. Fisher, A. A.: Med. Times **88**:1056 (Sept.) 1960. 3. Steller, R. E.: Antibiotic Med. & Clin. Therapy **7**:691 (Nov.) 1960. Literature on request.

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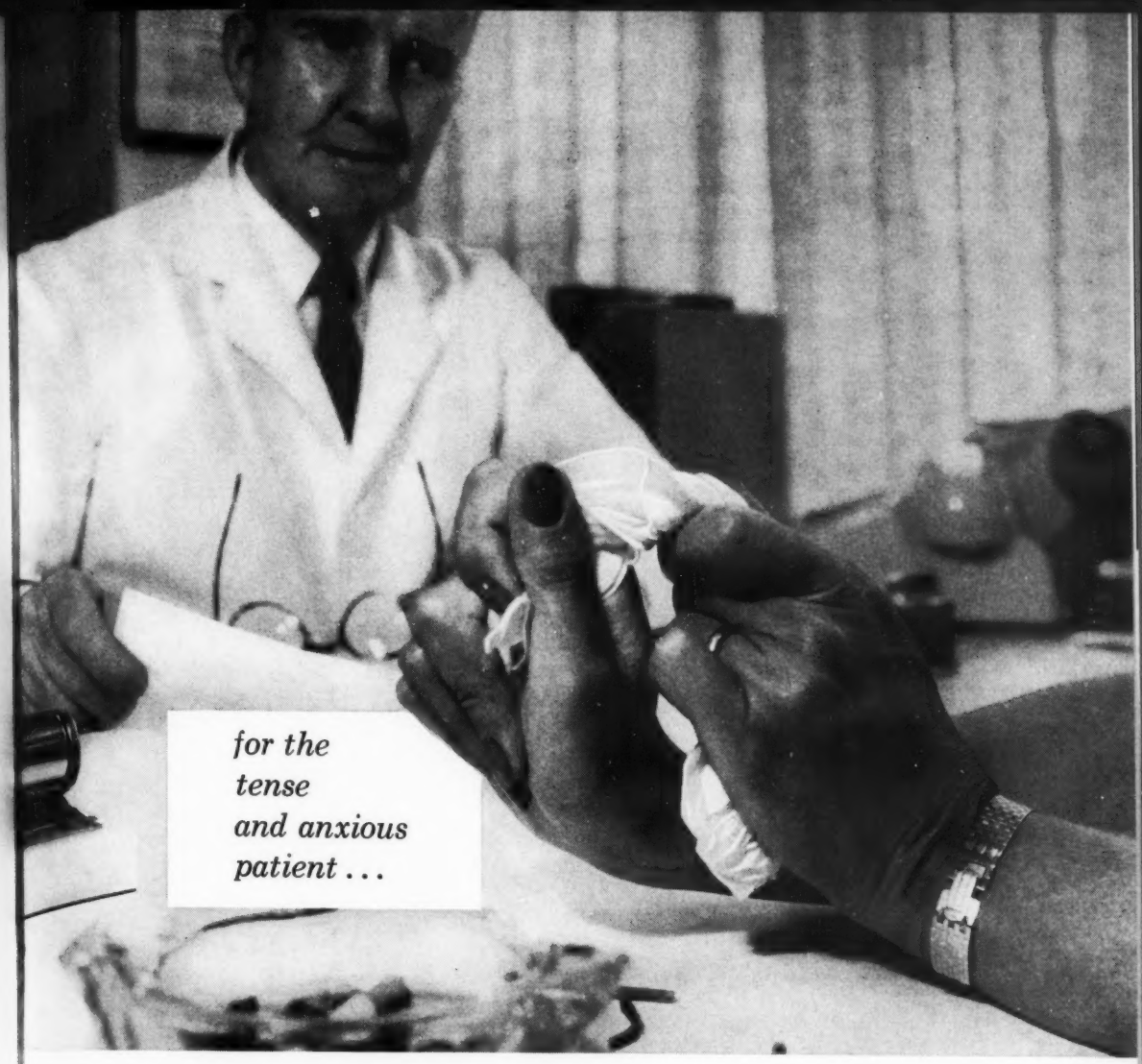

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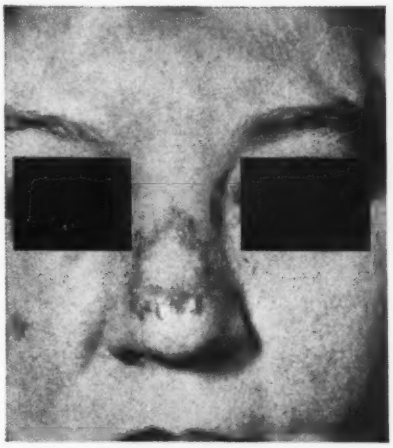

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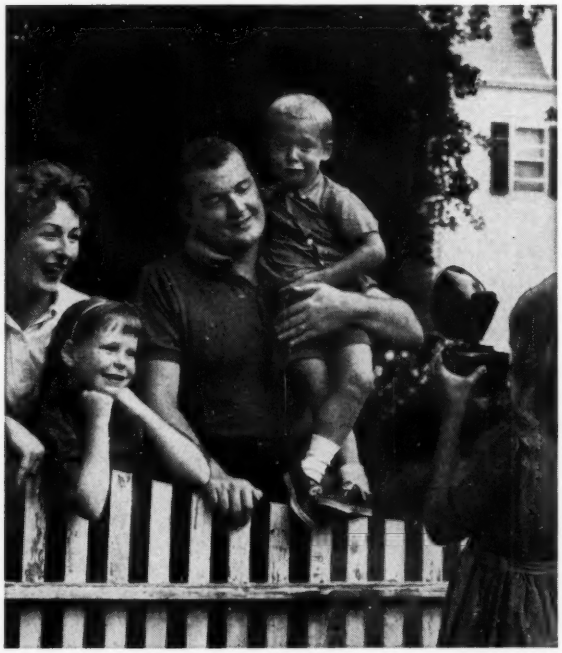

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Symposium on Immunologic Disorders & Transplantations	Allergy	Allergy	Pathology, Radiology & Urology* (TV)	General Practice	Symposium on Medicoeconomics	Symposium: When Disaster Strikes!
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Ophthalmology & Otolaryngology (TV 9-11 a.m.)	Dermatology & Syphilology	Neurology & Psychiatry	Surgery	Preventive Medicine	Urology	Orthopedic & Traumatic Surgery
	Gastroenterology	Plastic & Reconstructive Surgery	Medicine	Medicine	Obstetrics & Gynecology* (TV)	
	Obstetrics	Physical Medicine	Gastroenterology	Plastic & Reconstructive Surgery (TV)	Pediatrics	
	Neurology & Psychiatry	General Practice & Preventive Medicine*	Obstetrics	Industrial Medicine & Surgery		
	Ophthalmology & Otolaryngology	Gynecology	Industrial Medicine & Surgery	Ophthalmology & Otolaryngology		
	Pathology	Ophthalmology & Otolaryngology	Pathology	Orthopedic & Traumatic Surgery		
	Surgery and Plastic & Reconstructive Surgery*	Dermatology & Syphilology	Orthopedic & Traumatic Surgery	Radiology		
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	Urology					

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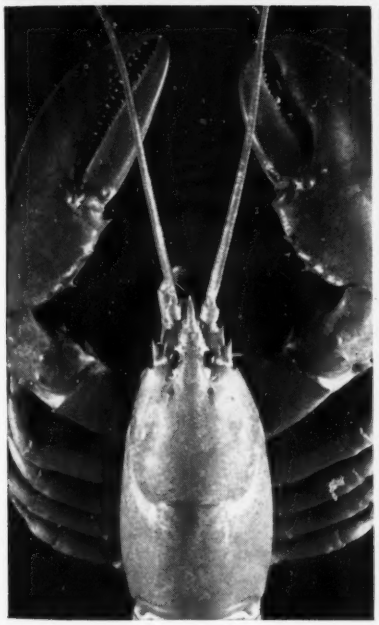

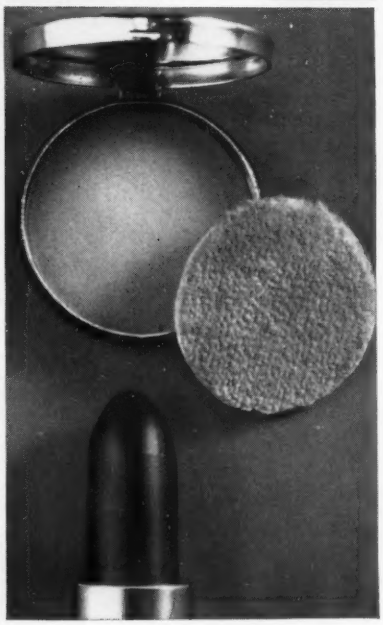

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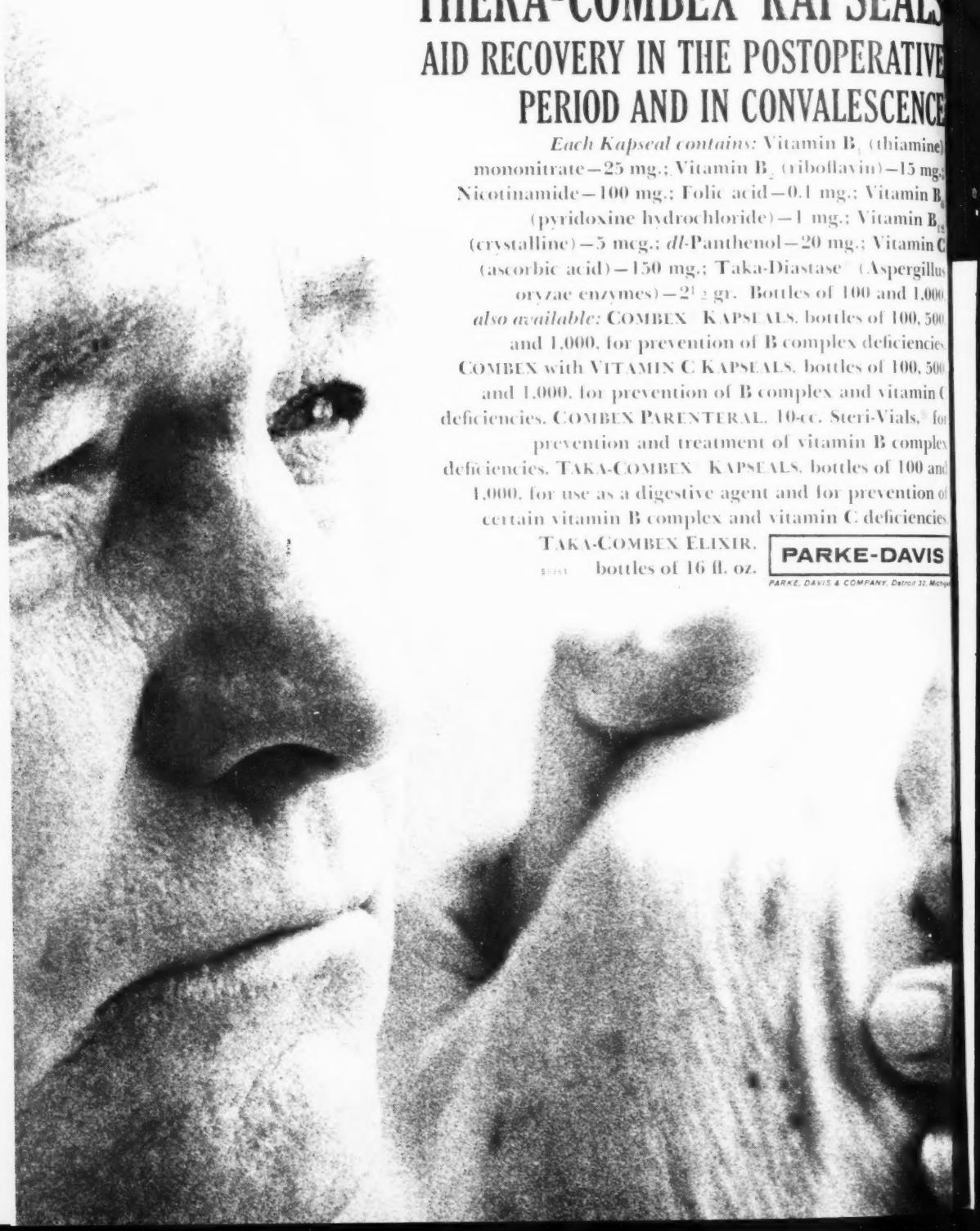
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